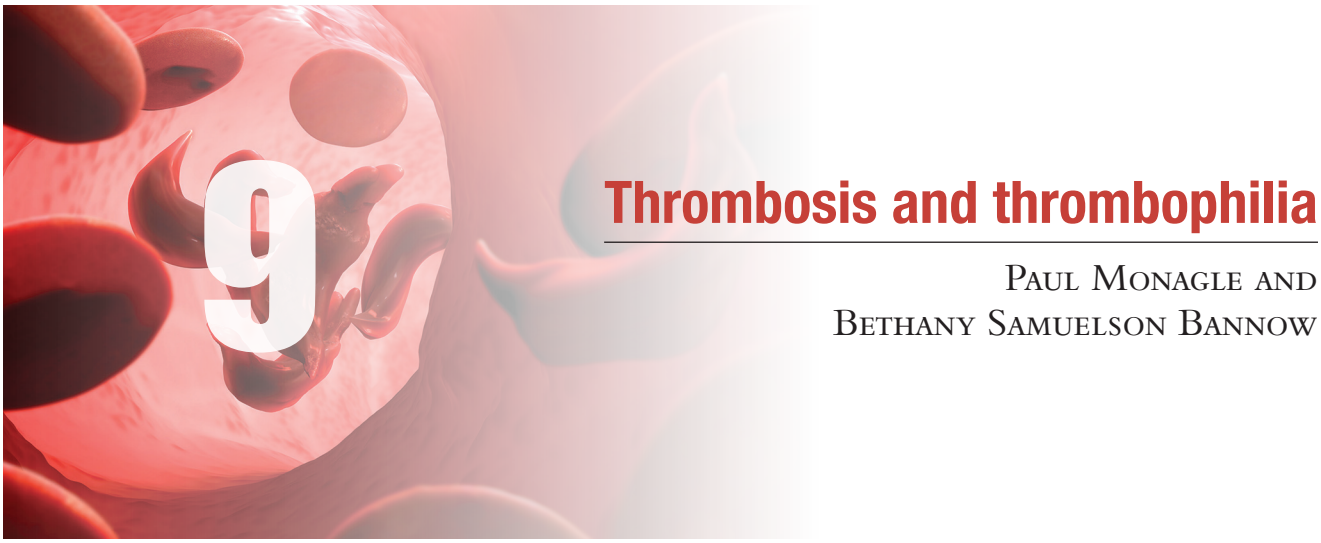

9 Thrombosis and thrombophilia

Paul Monagle and
Bethany Samuelson Bannow

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Introduction

This chapter reviews the epidemiology as well as various clinical, diagnostic, and therapeutic aspects of thrombosis; discusses the drugs used as antithrombotics; examines the pathophysiologic contributors to thrombosis; and describes the clinical relevance of inherited and acquired thrombophilias.

Venous thromboembolism

In adults, deep vein thrombosis/pulmonary embolism (DVT/PE) has an incidence of 2 to 3 per 1000 person-years. Estimates suggest that between 300,000 to 600,000 people in the United States develop DVT/PE each year, and venous thromboembolism (VTE) causes at least 60,000 to 100,000 deaths each year. The incidence increases with age, up to 2 to 7 per 1000 in those over the age of 70. Approximately half of DVT/PE episodes are hospital-associated, with VTE being a leading cause of disability-adjusted life-years lost.

In children, the incidence of VTE is 0.07 to 0.14 per 10,000. However, if one considers hospitalized children, the rate increases by 100 to 1000 times to at least 58 per 10,000 admissions. Therefore, despite some exceptions, venous thrombosis should be considered a disease of sick children. The most common age groups for VTE are neonates and teenagers, reflecting the pattern of associated underlying diseases and interventions. The most common precipitating factor is the presence of central venous access devices (CVADs), which are related to almost 90% of VTE in neonates and more than 60% in older children. Thus, a large proportion of VTE in children occurs in the upper venous system (subclavian veins, internal jugular veins, brachiocephalic veins) in accordance with placement of a CVAD.

Deep vein thrombosis of the leg and pulmonary embolism

Symptoms

The term *DVT* refers to thrombosis involving deep veins of either the leg (popliteal, femoral, and iliac) or arm (brachial, axillary, subclavian, and brachiocephalic). DVT of the pelvic and leg veins presents with varying degrees of leg swelling, pain, warmth, and skin discoloration. Symptoms are typically nonlocalized in the leg, and localized symptoms are more suggestive of a superficial thrombophlebitis.

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It is important to recognize that *proximal* DVT is defined as involving the popliteal or more proximal (eg, femoral or iliac) veins, whereas *distal* DVT involves vessels distal to the trifurcation of the popliteal vein. A palpable subcutaneous cord-like firmness is indicative of a superficial thrombophlebitis and is discussed in a separate paragraph. The onset of DVT symptoms can be sudden or subacute over days to weeks. DVT can easily be missed or misdiagnosed, as the symptoms can be nonspecific. PE presents with varying degrees of severity of shortness of breath, chest pain that is classically respiratory dependent, nonproductive cough, and hemoptysis. A massive PE can lead to sudden death. Small PEs are often asymptomatic and may be found incidentally on computed tomography (CT) imaging of the chest done for other reasons. There is no uniform definition for the severity or degree of PE. The definition can be either anatomic or physiologic. The physiologic one is preferred for treatment decision-making, as it is a better predictor of mortality. Any PE that causes hemodynamic instability (hypotension) is referred to as *massive PE*. *Submassive PE* is the term for PE associated with normal arterial blood pressure but right ventricular dysfunction that may be defined by electrocardiographic, echocardiographic, or CT criteria. Of note, in European guidelines (European Society Cardiology 2014) PE with hypotension is also referred to as high-risk PE, whereas PE with a high pulmonary embolism severity index score and signs of right ventricular dysfunction is called intermediate risk, further distinguished as intermediate-high and intermediate-low *risk* based on the presence of 2 or 1 features of right ventricular dysfunction, respectively. Patients without additional risk factors are then assessed as low-risk.

In children, the clinical presentations are similar, but for CVAD-associated VTE, loss of CVAD patency is a frequent earlier sign. Stroke secondary to paradoxical emboli can also be the primary presentation in children with right-to-left shunts, such as those with congenital heart disease or neonates with patent foramen ovale. Children often do not present with any acute symptoms, but rather long-term symptoms, including prominent collateral circulation in the skin over the related vessels, repeated loss of CVAD patency, repeated requirement for CVAD replacement, loss of venous access, CVAD-related sepsis, chylothorax, chylopericardium, and postthrombotic syndrome (PTS).

Pathophysiology of thrombosis

Thrombosis, defined as clotting beyond that required for physiological hemostasis, has 3 main causes, referred to as Virchow's triad: reduced blood flow (stasis), blood hypercoagulability, and vascular wall abnormalities. Under normal circumstances, if blood vessel integrity is interrupted, coagulation takes place and a blood clot forms to prevent excessive bleeding. However, blood in the intact vasculature is kept in a fluid state by multiple endogenous antithrombotic factors that include normal endothelium and anticoagulants. These natural anticoagulants, such as antithrombin (AT), protein C, and protein S, prevent excess thrombin formation. Once a thrombus has formed, its growth is limited by clot lysis, which eventually leads to thrombus resolution.

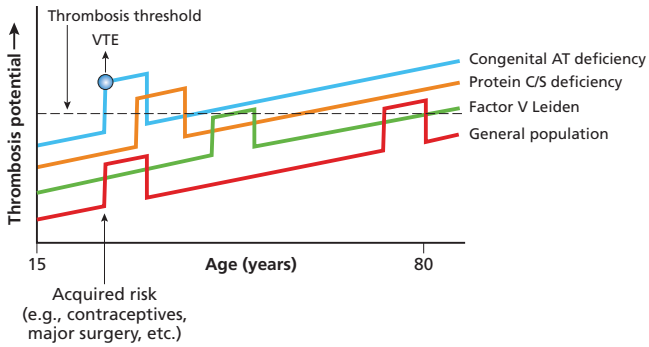

Figure 9-1 Threshold model of thrombosis risk. Adapted from Rosendaal FR, *Lancet*. 1999;353:1167-1173.

VTE is a typical multicausal disorder, with more than 1 factor (genetic or environmental) needed for thrombosis to occur. A pathophysiologic model suggests that each individual has a baseline (or background) thrombosis risk that increases with age (Figure 9-1). Transient risk factors, such as major surgery or estrogen therapy, temporarily increase a person's thrombosis risk, but the threshold of thrombosis formation often is not reached (Figure 9-1). Most people, therefore, never develop symptomatic VTE. However, the individual with a higher baseline thrombosis risk, such as a known or unknown inherited or acquired intrinsic predisposition to clotting (thrombophilia), may cross the thrombosis threshold while exposed to a transient risk factor and thus present with symptomatic VTE (Figure 9-1).

Thrombus formation in the cardiac ventricles and atria often is caused by stagnant blood flow in dyskinetic, or aneurysmal parts of the heart chambers or in fibrillating atria. These intracardiac thrombi arise in a low-flow environment and are thus pathophysiologically thought to be similar to the thrombi that lead to venous thrombosis.

Arterial clots usually form in areas of atherosclerotic vascular damage. The events leading to atherosclerosis—mainly lipid disturbances, oxidative stress, and inflammation—have been relatively well-studied. The composition and vulnerability of plaque to rupture, rather than the severity of stenosis, are the most important determinants

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for the development of acute arterial ischemic syndromes. Disruption of the fibrous cap or endothelium overlying an atheromatous plaque exposes collagen and tissue factor to the circulating blood, leading to platelet adhesion and aggregation and local thrombin formation, with subsequent partial or complete vessel occlusion.

In general, the hemostatic system in neonates is a balanced physiologic system despite low concentrations of plasma coagulation proteins with prolonged prothrombin time and partial thromboplastin time, counterbalanced by physiologically decreased levels of natural coagulation inhibitors. The coagulation system of children evolves with age, with marked physiological differences in the concentration of the majority of blood clotting proteins, a concept known as *developmental hemostasis*. Notably, there is evidence that children are protected from thrombosis from a number of different perspectives. Patients with congenital AT, protein C, or protein S deficiencies, or with activated protein C resistance may present early in life, but usually do not present with thrombosis until late teenage years or even later. In addition, VTE secondary to acquired risk factors occurs considerably less frequently in children compared to adults. Furthermore, children prior to puberty may undergo abdominal or trauma surgery without anticoagulant prophylaxis because secondary thromboses are rare.

Diagnosis of VTE

Because VTE is confirmed by objective testing in a relatively small percentage of patients presenting with possible DVT/PE, several clinical scoring systems (eg, Wells, Oudega, Hamilton, Geneva) have been validated in adults; by defining the pretest probability of disease, these scores help determine which diagnostic tests are most appropriate. Selected whole-blood or plasma D-dimer tests are well-evaluated and useful in the diagnostic workup for DVT and PE. In outpatients with a low pretest probability for DVT or PE, a negative test with a sensitive D-dimer assay reliably excludes VTE, and no further imaging study is needed. Outpatients with a low pretest probability for DVT or PE and a positive D-dimer test, and any patient with moderate or high pretest probability for DVT or PE, need to undergo imaging studies. Algorithms with adjustments of D-dimer threshold levels that prompt imaging studies have recently been validated, either based on age ("Age-ADJUST") or presence of specific items of the "YEARS" clinical prediction score (pregnancy, hemoptysis, clinical DVT/PE most likely diagnosis). The generalized application of D-dimer testing, however, is limited by the large number of different assays available, some highly sensitive and others less sensitive; the increase in baseline values with age, a lack of standardization of assays and widespread use in patients in whom this testing is not indicated, such as patients with a moderate or high pretest probability of disease, who should undergo objective testing irrespective of the result of their D-dimer. In children, the D-dimer test as a diagnostic tool for VTE has not been well-studied and available evidence does not support its use. The D-dimer test is of limited diagnostic utility in a variety of conditions (eg, pregnant patients, patients with cancer/or sickle cell disease) where it is known to be elevated at baseline.

Venous compression ultrasound (CUS) is the most widely used imaging study to look for DVT of the legs. Sensitivity and specificity of the test is operator dependent, especially for distal lower-extremity DVT, and an experienced ultrasound technician or physician is key in obtaining reliable results. It can be challenging, even for an experienced operator, to distinguish between acute versus chronic thrombus solely based on CUS. Magnetic resonance (MR) venography of leg or pelvic veins is a sensitive test to detect DVTs, but it is expensive and not widely available. Imaging with MR or CT venography may be necessary for upper-extremity DVT, particularly catheter-related events, because ultrasound may miss occlusion within the superior vena cava and brachiocephalic and subclavian veins because of interference of the clavicles and ribs. Ultrasound is the most common modality used in children; however, its validity should be carefully considered. The low pulse pressure in premature newborns likely makes CUS more difficult to interpret. Similarly, the presence of CVADs makes compressibility difficult to assess, which greatly reduces the sensitivity of CUS. The PAARKA study demonstrated ultrasound to have a sensitivity of 20% for intrathoracic thrombosis, yet diagnosed jugular thrombi that were missed on venography.

To diagnose PE, several imaging modalities exist: ventilation/perfusion (V/Q) scanning, chest CT pulmonary angiography (CTPA; also known as spiral CT, helical CT, or PE-protocol CT), chest MR angiography, and conventional intravenous contrast pulmonary angiogram. The V/Q scan is a well-validated imaging study. CTPAs are often preferred to V/Q scans because they are easier and faster to perform and have good performance characteristics. Conventional intravenous contrast pulmonary angiography, once considered the gold standard for the diagnosis of PE, now is rarely done because the test is invasive and not widely available. There is ongoing debate about the clinical significance of isolated subsegmental or smaller pulmonary artery filling defects that can be seen on chest CT scans, and the clinical relevance is likely

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dependent upon underlying conditions (eg, cancer) and clinical situation (hospitalized versus performed for cancer screening, for instance). There are a number of potential difficulties with interpreting V/Q scans in children. In children, following specific cardiac surgeries such as Fontan surgery, total pulmonary blood flow is not assessed by isotope injected into an upper limb. Injection into both upper and lower venous systems is required, but even then, the impact of intrapulmonary shunting may make interpretation difficult. In addition, there are concerns about the safety of perfusion scanning in children with significant right-to-left cardiac shunts, as likely significant amounts of macroaggregated albumin lodge in the cerebral circulation, and the impact of this is unknown. Repeated CTPA may cause significant radiation exposure to breast tissue in young female patients.

Acute therapy of VTE

Patients with acute VTE need to be anticoagulated to prevent the extension of thrombus and decrease mortality. Direct oral anticoagulants are preferred over vitamin K antagonists (VKAs) because of their lower risk of intracranial and fatal bleeding in patients without contraindications and without cancer. Treatment of cancer-associated VTE is discussed in a separate paragraph. Apixaban (higher initial dose for 7 days) and rivaroxaban (higher initial dose for 21 days) can be used to treat acute DVT or PE without prior parenteral therapy. Subcutaneous low-molecular-weight heparin (LMWH) or fondaparinux dosed based on body weight and intravenous unfractionated heparin (UFH) with activated partial thromboplastin time (aPTT) monitoring and dose adjustments are all effective and acceptable treatment options and need to be given for at least 5 days (overlapping with warfarin until the international normalized ratio [INR] is ≥2.0 on 2 consecutive occasions, or prior to starting dabigatran or edoxaban if 1 of these agents is used). In selected patients with extensive acute femoral or iliac DVT with symptom duration of <14 days and low bleeding risk, catheter-directed thrombolysis with or without mechanical thrombus fragmentation and aspiration can be considered to reduce acute symptoms. However, the ATTRACT trial showed that pharmacomechanical thrombolysis of femoral or iliac DVT, in addition to standard anticoagulation, leads to faster resolution of symptoms and improved canalization rates but does not improve the primary outcome measure of postthrombotic syndrome after 2 years.

Thrombolytic therapy in PE is indicated for massive life-threatening PE (ie, PE with hypotension caused by right ventricular dysfunction). However, patients with submassive or intermediate-high–risk PE (ie, those without hypotension but with right ventricular dysfunction) do not convincingly benefit from thrombolytic therapy because of the increased risk of major (including intracranial) bleeding. These patients require close monitoring, as rescue thrombolytic therapy seems beneficial in patients who develop cardiovascular collapse after initially being treated with anticoagulant therapy alone. Also, long-term (approximately 3 years) follow-up does not show benefit of thrombolysis in terms of persistent symptoms or complaints in patients with submassive or intermediate-high–risk PE. If thrombolytic therapy is given to a patient with PE, it is recommended that it be given systemically via a peripheral vein and with short infusion time, such as 2 hours. Catheter-directed thrombolysis for massive PE using lower doses of tissue plasminogen activator (tPA) is available in some centers, but there is no randomized controlled evidence showing that this is more effective or safer than systemic thrombolysis.

Outpatient management of patients with DVT and selected low-risk patients with PE has been shown to be safe, feasible, cost effective, and (if possible) is the preferred treatment of choice. Hospital admission is appropriate if either the patient is too sick to be managed at home or if social and financial circumstances make this the safer and more feasible option.

Patients with cancer have a strongly increased risk of VTE. Furthermore, they are at high risk of recurrence despite the use of therapeutic anticoagulants. LMWH (full therapeutic dose for the first 4 weeks, and 75% of therapeutic dose thereafter) has been shown to be more effective than VKAs in preventing recurrences in these patients and has been the recommended treatment for the first 6 months after the acute VTE. The Hosukai-Cancer VTE study showed that the factor Xa inhibitor edoxaban was noninferior to LMWH in the treatment of cancer-associated thrombosis (CAT), with a composite endpoint of recurrent VTE or major bleeding. An apparent greater efficacy was balanced against an increase in major bleeding, particularly from the gastrointestinal tract. The smaller Select-D study with rivaroxaban, from which patients with upper gastrointestinal tract cancers were excluded, showed similar results. The Caravaggio study reported recurrent venous thromboembolism occurred in 32 of 576 patients (5.6%) in the apixaban group and in 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio, 0.63; 95% confidence interval [CI], 0.37 to 1.07; $P < 0.001$ for noninferiority). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; $P = 0.60$).

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Recurrent VTE despite anticoagulant treatment

Treatment with therapeutic anticoagulants (ie, VKA, direct oral anticoagulant [DOAC], or therapeutic-dose LMWH), reduces the risk of extension or recurrence by 80% to 90%. In patients who fail anticoagulation, the clinician should remain vigilant for evidence of cancer, antiphospholipid syndrome (APS), or an anatomic cause of thrombosis. Clearly, issues with adherence should always be considered.

If a patient presents with recurrent VTE despite therapeutic anticoagulation, treatment options are either to increase the target INR (for patients on VKA), increase LMWH dose by 25%, add another anticoagulant or antiplatelet agent, or switch to another anticoagulant (particularly from VKA to LMWH). There are no robust data on the comparative effectiveness of the different anticoagulants or strategies in this setting.

Further pediatric considerations

The target therapeutic ranges for all anticoagulants are extrapolated from adult data, despite the known age-related differences in pharmacokinetics. LMWH is the preferred anticoagulant in children for the treatment of VTE because of its predictable pharmacokinetics, lack of interference with diet, and easy availability of anti-Xa assays for its monitoring. However, the need for twice-daily injections, and concerns related to bone density, limit its long-term use. Young infants (age < 2 months) require higher doses of LMWH and UFH. Dabigatran and rivaroxaban have both completed phase 3 trials, and are approved for treatment of VTE in children in Europe and USA. It is likely they will rapidly be used as oral alternatives to LMWH. Oral VKA therapy is a good option in children, provided there is adequate expertise and resources to support an outpatient anticoagulant management service that includes education of both child and parents. VKA management in young infants is challenging for several reasons: (1) physiologic reduction of vitamin K–dependent coagulant proteins, (2) excessive sensitivity to VKAs in breastfed infants, (3) resistance to VKA therapy resulting from vitamin K intake in infant formula, (4) lack of availability of liquid formulation in many countries, and (5) vascular access issues for INR monitoring. The use of home INR monitoring using capillary samples greatly increases the acceptability of VKA in all age groups. The experience of using fondaparinux is limited in children, but dosing regimens are available in children older than 1 year of age. When fondaparinux is used, it is monitored with anti–factor Xa assays. The 2012 American College of Chest Physicians guidelines provide details on dosing regimens and monitoring for specific anticoagulants.

Adjunctive therapies

Inferior vena cava filters

A clear indication for an inferior vena cava (IVC) filter exists only when a patient has acute proximal leg vein thrombosis or PE and has an absolute contraindication to anticoagulation. Retrievable filters should be used and removed as soon as clinically possible. Anticoagulant therapy should be initiated or resumed as soon as the patient's risk of bleeding permits. The presence of an IVC filter increases a patient's risk for recurrent DVT and confers a risk of caval vein thrombosis. When making a decision on the length of anticoagulant therapy in a patient with a permanent IVC filter, the presence of the IVC filter should be viewed as a risk factor for recurrent VTE.

Venous stents

May-Thurner syndrome is the term used for the chronic compression of the left common iliac vein between the overlying right common iliac artery and the fifth lumbar vertebral body posteriorly. Varying degrees of vein narrowing with this anatomic variant are common in the general population. If May-Thurner syndrome is demonstrated on venography or magnetic resonance imaging (MRI) in the patient with left-leg femoral or iliac DVT who successfully has received thrombolytic therapy, correction of the stenosis using balloon angioplasty and stenting can be considered, although there is no high-quality evidence that such interventions reduce the risk of recurrent VTE or PTS.

Although there are no clinical trials to determine their efficacy, venous stents are sometimes placed in other locations, either in the acute DVT context of catheter-directed thrombolysis, or to alleviate severe PTS—the right and left pelvic veins for post thrombotic vessel narrowing and scarring, and the superior vena cava and central arm veins in central venous catheter-associated strictures. Of note, the best long-term management of patients who have venous stents is not known, because of a lack of high-quality prospective studies examining their long-term patency with and without antiplatelet drugs or anticoagulants. Because stents are foreign bodies in the venous system and may lead to flow disturbances, it is possible that they have some prothrombotic risk. In addition, endothelial cell proliferation within stents is known to occur, potentially leading to stent stenosis and occlusion. In view of the limited data available, it may be best to see the presence of a venous stent as a potential risk factor for recurrent VTE.

Duration of anticoagulant therapy

The risk of recurrent VTE depends on the presence of risk factors, either transient or persistent, during the first

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Table 9-1 Considerations when discussing time-limited versus long-term anticoagulation therapy in adult patients with unprovoked VTE

Clinical factors that favor extended anticoagulant therapy
History of recurrent VTE
Male sex
Patient had a PE, not a DVT
D-dimer on anticoagulant therapy elevated at 3 or 6 months*
D-dimer elevated after having been off anticoagulants for 4 weeks*
Obesity
Older age
Persistent underlying risk factor such as active cancer or inflammatory bowel disease
Anticoagulant therapy well tolerated (with good INR control, if on VKA)
Little or no impact of anticoagulant therapy on patient's lifestyle
Patient's preference is to continue treatment
Patient has a known, strong thrombophilia (either congenital or acquired)
Factors favoring limited duration of anticoagulation
Female sex
Distal DVT or superficial venous thrombosis only
D-dimer negative after having been off anticoagulation for 4 weeks (most relevant to women)
No signs of PTS (most relevant to women)
Occurrence of bleeding complications or significant risk for bleeding
Patient's preference is to be off anticoagulants

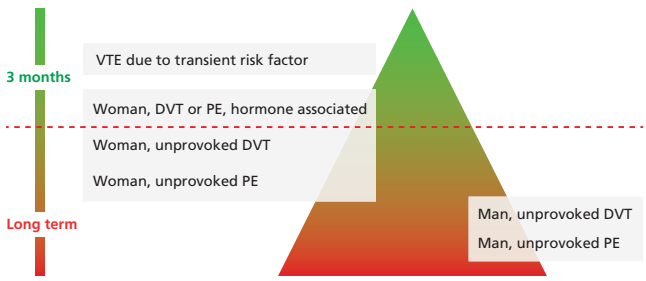
*Cutoff is assay specific (not all D-dimer assays have been studied for this purpose; clinicians should check with their local laboratory).

VTE. In patients with a VTE secondary to a major transient (reversible) risk factor, the risk of recurrence is low. Therefore, time-limited anticoagulation for 3 months is recommended. For patients with unprovoked proximal leg DVT or unprovoked PE in whom risk factors for bleeding are absent and for whom good anticoagulation control is achievable, long-term (extended) anticoagulation therapy should be strongly considered. Unselected patients who stop anticoagulants after some initial (eg, 3- to 12-month) period of treatment for unprovoked VTE have a 3-year recurrence rate of 20% to 30%; at 5 years these numbers are approximately 40% and 50%. Several parameters can be used in an effort to individualize the risk of recurrence (Table 9-1). This, along with the patient's bleeding risk factors and personal preferences, should be used to help the patient make an informed decision about whether to continue therapy (Figure 9-2). When extended anticoagulation therapy is chosen, the risks, benefits, and burdens should be reevaluated periodically (eg, once yearly). For patients with a first episode of unprovoked distal (ie, below the trifurcation of the popliteal vein) leg DVT, 3 months of anticoagulant therapy is recommended.

To aid decision-making about which patients continue or discontinue anticoagulation, there are risk scores created using data from VTE trials in which the rate of recurrent VTE was recorded and subgroup analyses were performed. Male sex is associated with a higher risk of recurrence; in women, the absence of PTS, a low D-dimer (measured after stopping anticoagulation for 4 weeks), and possibly a body mass index < 30 kg/m^2 predict a lower risk of recurrence. Of note, ultrasound appearance at diagnosis does not predict risk of recurrent thrombosis and thus should not be used as a guide to duration or intensity of therapy in adults. Nonresolution is not an indication for extended duration therapy. Low-dose apixaban (2.5 mg orally twice per day) or rivaroxaban (10 mg orally daily) decreases the incidence of recurrent VTE after the use of higher doses for 6 months, is more efficacious than low-dose aspirin at decreasing recurrent VTE, and is associated with a low overall risk of bleeding. Patients who choose to discontinue anticoagulation or have no access to DOACs but are still at some risk for recurrent VTE should be informed that daily low-dose aspirin is relatively safe and appears to reduce the likelihood of DVT/PE by about 30%.

Duration of anticoagulation in children is essentially extrapolated from adult data. Provoked VTE is usually treated for 3 months or until the risk factor (eg, CVAD) is removed. Many clinicians treat neonates or young infants for 6 weeks only if there is total radiological resolution of thrombus, and the validity of this approach

Figure 9-2 Management strategy regarding length of anticoagulation therapy decisions in patients after a first episode of provoked or unprovoked proximal VTE.


3 months
Long term
VTE due to transient risk factor
Woman, DVT or PE, hormone associated
Woman, unprovoked DVT
Woman, unprovoked PE
Man, unprovoked DVT
Man, unprovoked PE
Other considerations: bleeding, lifestyle impact, patient preference, adherence to treatment

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is supported by the recently reported Kids-DOTT (Duration of Therapy for Thrombosis) trial. The optimal duration of therapy for unprovoked VTE is unknown and the impact of anticoagulation on the patient's lifestyle and mental health, as well as patient preferences, are significant considerations.

Postthrombotic syndrome

PTS may be caused by several factors, including incompetent venous valves damaged by the thrombus, associated inflammatory mediators, and impairment of venous return because of residual venous obstruction from incompletely cleared thrombus. Fewer than 5% of DVT patients develop severe PTS (sometimes referred to as postphlebitic syndrome) within 1 to 2 years of the acute DVT, in most cases. However, up to 30% of patients experience symptoms of mild to moderate PTS. Symptoms and signs include chronic extremity swelling, pain, heaviness, fatigue, paresthesias, skin induration, dryness, pruritus, erythema and chronic dark pigmentation, and skin ulcers, in severe cases. The risk for developing PTS was previously believed to be decreased by wearing graduated compression stockings (40 mm at ankle, 30 mm at midcalf) for 2 years after an acute DVT, but placebo-stocking randomized controlled trials have since failed to demonstrate an impact of this intervention on the risk of PTS. Treatment options for patients with PTS are limited. Compression stockings should be worn if they provide symptom relief. In patients with significant leg swelling, imaging of leg veins with Doppler ultrasound and of the pelvic veins with CT or MR venography can be considered to evaluate for focal pelvic vein obstruction or narrowing caused by May-Thurner syndrome or postthrombotic scarring. Although these sorts of anatomic abnormalities might be amenable to pelvic vein angioplasty and stenting, there is no high-quality evidence to support the efficacy or safety of such interventions in this challenging clinical situation. Finally, a home compression pump with compression sleeve for the affected leg can be considered for patients with significant symptoms. In children, the challenge is often to get appropriately fitted stockings or sleeves for use in upper limbs. The next challenge is to get the children to wear them. There are no effective studies and management is extrapolated from adults.

Pulmonary hypertension

Pulmonary hypertension caused by VTE, termed *chronic thromboembolic pulmonary hypertension* (CTEPH), is defined as an elevated mean pulmonary artery pressure of >25 mm Hg (without evidence of left-heart failure) and occurs in 1% of patients with acute PE after 6 months. CTEPH can be the result of a single or recurrent episodes of PE. The patient who experiences chronic shortness of breath or significant generalized malaise after PE should be evaluated for pulmonary hypertension. A formal 6-minute walk test with pre- and postexercise pulse oximetry measurements is appropriate. Chest CT angiogram findings may be minimal with chronic distal PE. A V/Q scan is more sensitive for chronic PE. Echocardiography can be used to estimate pulmonary artery pressure. Right-heart catheterization with pulmonary artery pressure measurements then defines the degree and etiology of hypertension, and pulmonary arteriography allows assessment of whether potentially curative pulmonary endarterectomy is indicated, although only performed in specialized centers. Long-term anticoagulant therapy is indicated. Pharmacologic therapy specific for pulmonary hypertension, such as bosentan (an endothelin receptor antagonist), can be considered in inoperable patients, following assessment in specialized centers.

Primary prevention of VTE

Prophylaxis against VTE should be considered in every hospitalized patient based on an individual patient's risk stratification. Detailed prophylaxis guidelines for all types of patients have been published in the medical literature, most notably the ASH guidelines. Formal VTE prophylaxis protocols should be in use in all hospitals. The most convincing evidence of net benefit from VTE prophylaxis comes from surgical populations.

If anticoagulation for VTE prophylaxis is appropriate, several options are available: (1) LMWHs at once- or twice-daily intervals, (2) fondaparinux once daily, (3) VKAs, or, in patients undergoing total knee or hip replacement, (4) apixaban or rivaroxaban can be used. United States Food and Drug Administration (FDA)-approved indications vary between the different pharmacological options. There is evidence that aspirin and other antiplatelet agents provide protection against VTE in hospitalized patients at risk, especially after initial anticoagulation. In the specific setting of total hip or knee replacement, a recent randomized trial showed, after an initial 5 days of 10 mg of rivaroxaban, noninferiority of low-dose aspirin compared to rivaroxaban for an additional 9 (after knee replacement) to 30 days (after hip replacement) for postoperative VTE. Prophylaxis may be given only during the hospitalization or, if the VTE risk persists after discharge home, for an extended period of time. The net benefit and cost effectiveness of postdischarge prophylaxis (up to 5 weeks), are well established in patients after hip fracture, hip replacement, total knee replacement, and major cancer surgery.

Mechanical methods of prophylaxis with graduated compression stockings or intermittent pneumatic

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compression devices typically are recommended for patients who are at high risk for bleeding or as an adjunct to anticoagulant-based prophylaxis.

Pediatric consideration

There is growing concern about rising prevalence of VTE in hospitalized children, but the role of pharmacological thromboprophylaxis in preventing hospital-acquired CVAD-related thrombosis is controversial. While CVAD is the most common risk factor for VTE, it is estimated that less than 2% of children with CVAD get symptomatic VTE. Better risk stratification algorithms and the risk-benefit ratios of therapy need to be determined.

The studies performed to date of primary prophylaxis of hospitalized children suggest that prepubertal hospitalized children rarely require thromboprophylaxis. Postpubertal children with multitrauma, sepsis, or hypotension may require thromboprophylaxis in the presence of additional risk factors such as obesity (>95th percentile or body mass index > 30), oral contraceptive pill use, dehydration, estimated length of stay > 4 days, family history of VTE, known thrombophilia, and CVAD. Similarly, in postpubertal children having prolonged surgery, early ambulation, calf compression, and the use of elastic compression stockings are likely adequate unless there are additional risk factors as outlined previously and strict bed rest enforced for >4 days. For these in-hospital children, once-daily enoxaparin is most commonly used if pharmacological prophylaxis is required.

Anticoagulation prophylaxis with oral VKA therapy is currently recommended for children receiving long-term home total parenteral nutrition on the basis of small numbers of cohort studies.

Much more work has focused on primary prevention in pediatric cardiac surgical populations. Modified Blalock-Taussig shunts, and Fontan procedures in particular, have been the focus of a number of studies. Cardiomyopathies, pulmonary hypotension, and prosthetic cardiac valves are all common indications for primary prophylaxis. While there is general agreement that prophylaxis is worthwhile and any prophylaxis reduces the thrombosis risk, the optimal agent, dose intensity, and duration remain unclear.

Superficial thrombophlebitis and unusual site venous thromboses

Superficial thrombophlebitis

Superficial thrombophlebitis in the legs refers to the peroneal, posterior tibial, and saphenous veins. In the upper extremities it refers to antecubital, basilic, and cephalic veins. Risk factors concur with those for VTE; and in addition, varicose veins, intravenous catheters or phlebotomy, or septic thrombophlebitis are commonly associated. Superficial vein thrombosis (SVT) also occurs in association with thromboangiitis obliterans (Buerger's disease) and Behçet's disease. The term *Trousseau syndrome* often is used for migratory thrombophlebitis in patients who subsequently are diagnosed with cancer, but the term is not well or uniformly defined.

Extension of superficial thrombophlebitis into the deep venous system of the leg occurs in about 1 in 6 patients with extensive superficial thrombophlebitis and often is present at time of diagnosis. To rule out concomitant DVT or extension, CUS should be performed at diagnosis, and follow-up CUS should be considered in patients with extensive superficial thrombophlebitis for whom anticoagulation is not prescribed.

Patients with extensive or recalcitrant superficial thrombophlebitis benefit from a short course of out-of-hospital anticoagulant therapy, such as 6 weeks of subcutaneously administered fondaparinux, low-dose DOAC, or LMWH. Prophylactic dose fondaparinux (2.5 mg daily) for 45 days, in comparison to placebo, has been shown to reduce the risk of DVT and SVT extension and SVT recurrence. The number needed to treat to prevent 1 clinically important event is 20, and for symptomatic DVT or PE 88, which has led to debates regarding the cost effectiveness of routinely anticoagulating patients with superficial thrombophlebitis. A recent randomized controlled trial that compared 10 mg rivaroxaban with 2.5 mg fondaparinux showed that fondaparinux was associated with a non–statistically significant reduction of symptomatic VTE, DVT, recurrence of SVT, mortality, clinically relevant nonmajor bleeding, serious adverse events, or adverse effects of treatment compared with rivaroxaban. For LMWH, there is only low-quality evidence regarding the optimal dosing and the duration of therapy, without showing a reduction in symptomatic VTE. Thrombophlebitis that is not very extensive (ie, <5 cm in length and not close to the deep venous system) requires only symptomatic therapy, consisting of analgesics, anti-inflammatory medications, and warm or cold compresses for symptom relief, although the evidence is very limited and does not inform clinical practice about the effects of these treatments in terms of VTE.

Upper-extremity DVT (and catheter-related thrombosis)

The superficial veins of the arm include the antecubital, cephalic, and basilic veins. The deep venous system includes the brachial vein, which becomes the axillary vein, followed by the subclavian and brachiocephalic

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veins, and finally the superior vena cava. Upper-extremity DVTs make up 1% to 4% of all DVTs in adults. In adults, roughly 80% are secondary to central venous catheters and cancer, and 20% are primary events; however, these data depend largely on which patient population is studied. Doppler ultrasound (sensitivity 78% to 100% and specificity 82% to 100%), contrast venography (gold standard), and CT or MR venography are the tools used to diagnose upper-extremity thrombosis. In adults, the risk of PE with upper-extremity DVT is not well defined and depends on the modality used to detect it but seems to be low (especially if the clot is catheter-associated). Postthrombotic syndrome is common; residual thrombosis and axillosubclavian vein thrombosis appear to be associated with a higher risk of upper-extremity PTS, whereas catheter-associated DVT may be associated with a lower risk. These associations are less clear in children.

Management for DVT of the upper extremity consists of the following: (1) LMWH, UFH, or fondaparinux in the acute setting; (2) continued anticoagulation for at least 3 months for unprovoked DVT or catheter-associated DVT; and (3) no catheter removal in patients with DVT associated with a central venous catheter if the catheter is functional and still needed. In children, especially those with right-to-left shunts, a period of anticoagulation prior to catheter removal is frequently advocated to reduce the risk of paradoxical embolus at the time of removal. A DOAC is likely effective in upper-extremity DVT and, although these agents have not been studied in catheter-associated thrombosis in adults, the results of large, prospective randomized controlled trials of DOACs in the treatment of VTE support their consideration in the acute and long-term treatment of noncancer patients with catheter-related upper-extremity DVT. Decisions about duration of therapy for upper-extremity DVT usually are based on information extrapolated from studies of patients with lower-extremity DVT or PE. For catheter-associated DVT, a brief period (4 to 12 weeks) of anticoagulation after catheter removal is likely sufficient. There is little or no direct evidence to support any particular duration of anticoagulant therapy after a first unprovoked (or catheter-associated) upper-extremity DVT.

Upper-extremity DVTs may be caused by thoracic outlet syndrome, also referred to as effort thrombosis, thoracic outlet syndrome, or Paget-Schroetter syndrome. This is because of compression of the axillary vein by pressure from the clavicle, an extra rib, or enlarged or aberrantly inserted muscles, often provoked or potentiated by abduction of the arm and repetitive arm movements. Younger athletes are often affected. There is no uniform approach to treatment of these patients. Management options include anticoagulation, thrombolytic therapy, angioplasty with or without stent placement, thoracic outlet surgery with rib or soft tissue resection, and surgical resection of the focally narrowed vein with vein reconstruction. Individual treatment decisions need to be made, and a team approach that includes vascular medicine, vascular surgery, and interventional radiology may be appropriate.

Hepatic vein thrombosis

Hepatic vein thrombosis, also referred to as Budd-Chiari syndrome, has varied clinical presentations, ranging from asymptomatic to fulminant liver failure. A cause can be identified in approximately 84% of patients. The most common risk factor is myeloproliferative neoplasms (MPNs) (49% of patients). Polycythemia vera accounts for 27% of cases; essential thrombocytosis (ET) and primary myelofibrosis are less-prevalent causes. The *JAK2* mutation is present frequently in patients with the syndrome (29% of cases), even if no hematologic abnormalities suggestive of an MPN are present. Paroxysmal nocturnal hemoglobinuria (PNH) should also be considered.

The diagnosis is made by Doppler ultrasonography, contrast-enhanced CT scanning, or MRI. In the acute setting of fulminant thrombosis, thrombolytic therapy can be considered. Angioplasty of narrowed or occluded hepatic veins can be performed, shunt procedures may be required, and liver transplantation may be necessary. Anticoagulation is usually appropriate and often is given long term, typically with VKAs. INR monitoring may be problematic, however, because liver synthetic dysfunction may lead to a baseline elevation of INR even before VKA therapy. Alternative monitoring tests for VKAs, such as factor II or X activity, may have to be used. Also, treatment with LMWH, fondaparinux, or a DOAC instead of VKAs can be considered. Hepatic vein thrombosis is rare in children outside of post liver transplant.

Portal vein thrombosis

Portal vein thrombosis (PVT) often is silent and may be discovered only upon evaluation of a variceal gastrointestinal bleed. It is associated with cirrhosis, the MPNs, *JAK2*-positive status without overt MPN, PNH, intra-abdominal neoplasia or inflammation, infection, trauma, and surgery.

In newborns, PVT most commonly occurs secondary to umbilical vein catheterization, with or without infection. The most common cause of PVTs in older children is post liver transplant, although cases associated with intra-abdominal sepsis, splenectomy, sickle cell anemia, and the presence of antiphospholipid antibodies (APLAs) are reported. In approximately 50% of children, an underlying

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etiology is not identified. In contrast to adults with PVT, liver function is usually normal in children. Diagnosis typically is made by Doppler ultrasonography. CT or MR venography also can provide evidence that PVT is present. Cavernous transformation of the portal vein reflects old PVT, as do collaterals in the porta hepatis. In the patient with acute PVT, extension of thrombus into the mesenteric veins may occur and lead to intestinal infarction and the need for surgical bowel resection. The patient with acute PVT typically is anticoagulated for at least 3 to 6 months to prevent progression of thrombosis. Regarding long-term anticoagulation therapy in these patients, as well as in patients with incidentally discovered PVT, the risk of bleeding has to be balanced individually against the risk of rethrombosis.

Mesenteric vein thrombosis

Venous drainage of the intestine is via the superior mesenteric vein (SMV) and inferior mesenteric vein (IMV) into the portal vein. SMV thrombosis, if diagnosed late, leads mostly to small bowel ischemic changes. The very rare IMV thrombosis may lead to ischemia in the sigmoid colon. Mesenteric vein thrombosis (MVT) may be caused by trauma, surgery, intra-abdominal infections, inflammatory bowel disease, pancreatic disease, and progression of PVT, but also may occur spontaneously, particularly in patients with MPNs, presence of the *JAK2* V617F mutation, and PNH. Symptoms are vague, often leading to a delay in diagnosis of days to weeks, such that the patient presents as a surgical emergency with ischemic bowel. The principal cause of a high mortality rate in MVT is a delay in diagnosis. Preoperative diagnosis is made by CT angiography. Doppler ultrasound may be diagnostic, but it is operator dependent and may have limited sensitivity, particularly in the obese patient. Once diagnosed, patients are managed with anticoagulation alone or in combination with surgical intervention. Most patients improve. Decisions on length of anticoagulant therapy depend, as with most of the other VTE disorders, on the triggers for the thrombotic episode and other persistent underlying risk factors. Length of treatment is at least 3 months, but may have to be long-term.

Splenic vein thrombosis

Because of the intimate anatomic contact of the splenic vein with the pancreas, the main causes of splenic vein thrombosis are pancreatitis and pancreatic malignancies. Similar to MVT, intra-abdominal problems (infection, surgery, and trauma) also play a role in the etiology. Symptoms often are subtle, and the diagnosis is not infrequently a coincidental discovery on abdominal imaging studies done for other reasons. The need for, and length of anticoagulant treatment is not well defined. Splenic vein thrombosis is frequently observed after splenectomy and is likely a physiological adaptation to the presence of a blind venous "stump." It is generally not felt to be an indication for anticoagulation.

Cerebral and sinus vein thrombosis

Thrombosis of the cerebral, cortical, and sinus veins often is referred to as *cerebral sinovenous thrombosis* (CSVT). It occurs in 1 to 2 cases per 100,000 in the general population, about 3 times as often in women than in men, because of the strong association with sex-specific risk factors such as oral contraceptive use, pregnancy, and postpartum period. Unlike VTE at other locations, less than 10% of adults are older than 65. Approximately 80% of adults recover without functional disability, but early mortality does occur because of transtentorial cerebral herniation. Most neonatal CSVT occurs during the first week of life and seizures are the most common presenting symptom. Altered consciousness and focal motor deficits are other common symptoms. A significant group of infants may have relatively little in terms of specific neurological signs but may have nonspecific symptoms such as apnea, irritability, poor feeding, hypotonia, or vomiting. The etiology of neonatal CSVT remains unclear.

The presentations of CSVT can be subtle and varied. Seizures, loss of consciousness or altered consciousness, focal neurological deficits, headache, and symptoms of raised intracranial pressure have all been reported. Some children are in fact asymptomatic and CSVT is discovered on central nervous system (CNS) imaging that was performed for other reasons.

The cause of CSVT in many children remains unknown; however, many cases are associated with local infections/inflammation. Otitis media and mastoiditis can be associated with sigmoid and transverse sinus thrombosis. Severe dehydration or systemic illness (viral, bacterial or inflammatory) can be associated, despite no apparent direct link, to the cerebral circulation. CSVT is a common site for thrombotic complications in children with leukemia, especially when treated with L-asparaginase.

In adults, the most frequent but least specific symptom is severe headache, either of subacute or acute onset, present in 90% of patients; about 40% have seizures. Routine noncontrast and contrast head CT scans and brain MRI scans often are unrevealing, resulting in missed diagnoses, unless CT venogram or MR venogram is requested specifically.

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Approximately 40% of patients with CSVT have a hemorrhagic infarct, which is a consequence of venous occlusion. LMWH, or alternatively UFH if neurosurgical decompression is anticipated, is recommended (American Heart Association [AHA]/American Stroke Association 2011, European Federation of Neurological Societies 2010) in acute CSVT, even if some parenchymal hemorrhage is present. Currently, there is no available evidence from randomized controlled trials regarding the efficacy or safety of systemic or local thrombolytic therapy in CSVT. In a minority of patients in whom large venous hemorrhagic infarcts result in brain displacement and herniation, decompressive surgery is the only life-saving option. The role for DOACs is not defined, although small case series have been published with good results. After a first episode of CSVT, expert guidelines recommend anticoagulation for: (1) 3 months if the thrombosis was associated with a transient risk factor, (2) 6 to 12 months if the event was unexplained and no high-risk thrombophilia has been detected, and (3) long term if a high-risk thrombophilia is detected or the event is recurrent.

There is significant variation in treatment of neonatal CSVT, most likely related to uncertainty about the true risk of bleeding when neonates with CSVT are given anticoagulation therapy. The American College of Chest Physicians guidelines suggest anticoagulation for all affected neonates unless there is substantial intracerebral hemorrhage. Alternatively, the AHA guidelines suggest monitoring with sequential imaging and anticoagulation only in the presence of thrombus progression. In general, anticoagulation is an accepted component of therapy for all childhood CSVT, but this must be managed around any early surgical interventions that are required. Many authors suggest the use of anticoagulation in the presence of hemorrhage unless it is severe; the amount of hemorrhage that should preclude anticoagulation is not well delineated and it is probably better to err on the side of caution. In neonates and children, initial UFH transitioning to LMWH is the most common therapy and durations are similar to adults. However, rivaroxaban has also been shown to be very effective. There is little evidence to support thrombolysis.

Renal vein thrombosis

In adults, the classical symptom triad of acute renal vein thrombosis (RVT)—namely, acute flank pain, hematuria, and sudden deterioration of renal function—is uncommon. More common is a chronic course with subtle worsening of renal function, progressive proteinuria, and edema, often without pain or hematuria. Diagnosis is made by Doppler ultrasound or MR venography. Thrombolytic therapy should be considered in case of acute thrombosis, particularly if there is bilateral disease or impending renal failure. Anticoagulation therapy is indicated. The length of anticoagulant therapy depends upon whether the thrombotic event was associated with a transient prothrombotic risk factor or the patient has permanent risk factors.

RVT in neonates is the most common type of spontaneous venous thrombosis. Infants of diabetic mothers are at particular risk, but perinatal asphyxia and dehydration are also associated. Outside of the neonatal period, RVT is uncommon in children. The pathogenesis of this entity is not vascular access–related and studies indicate that the thrombotic process begins in the renal microvasculature and then extends out into the renal veins and potentially the IVC (in 50% to 60% of cases). This is important because it means the kidney damage, which is usually the cause of acute death from renal failure (3% in untreated patients) or the cause of long-term renal impairment (75%) or hypertension (15%), is unlikely to be resolved by removal of the large vessel thrombosis within the IVC or renal veins, as would be achieved by thrombectomy. Approximately 25% of cases are bilateral, supporting the concept that this disease is related to something occurring within the renal parenchyma vasculature as distinct from large vessels. Recurrence rates are very low, and subsequent risk of other thrombosis does not appear to be increased. Anticoagulation is recommended in unilateral disease with or without extension into the IVC, and thrombolysis should be considered in bilateral disease with renal impairment. While the evidence quality is low, treatment appears to give reductions in mortality and long-term hypertension.

Retinal vein thrombosis

Thrombosis can occur as central retinal vein occlusion (CRVO) or as branch retinal vein occlusion. CRVO has a prevalence of 1 in 250 to 1000 in individuals over 40 years of age. The presence of classic arterial cardiovascular risk factors, such as hypertension, hyperlipidemia, and especially diabetes, has been associated with retinal vein occlusion. An association with inherited or acquired thrombophilia has not been convincingly demonstrated. Unfortunately, there is very little high-quality evidence on which to judge the utility of antiplatelet or anticoagulant therapy for CRVO. One small (67-patient) randomized trial indicated that 90 days of LMWH treatment may be more effective than aspirin for the prevention of visual loss in patients with retinal vein occlusion; however, the optimal duration of anticoagulant therapy is not known.

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Arterial thromboembolism

General comments

The hematologist typically does not get called upon for the management of patients with ischemic disease that is caused by arteriosclerosis. Therefore, this chapter does not discuss the pathophysiology of arteriosclerosis and its role in arterial occlusive disease or the management approaches aimed at modifying an individual's arteriosclerosis risk factors.

Arterial thrombosis in the absence of arteriosclerosis

Arterial thromboembolic events in the young person (<50 years old) are rare, unless significant arteriosclerosis risk factors are present. No matter which territory the arterial thrombotic event occurs in, a number of risk factors and associated disorders should be investigated to clarify the etiology of the event (Table 9-2). As for specific arterial territories, in the case of upper-extremity arterial thromboembolism, thoracic outlet syndrome should be considered; in lower-extremity claudication or arterial thromboembolism, popliteal artery entrapment syndrome, cystic adventitial disease of the popliteal artery, fibromuscular dysplasia of the lower-extremity arteries, and endofibrosis of the iliac artery should be considered; and in the case of stroke, spontaneous or traumatic cervical artery dissection should be considered.

Arterial thrombosis is a classifying clinical criterion for APS. Whether young patients with otherwise unexplained arterial thromboembolic events and an inherited thrombophilia (such as protein C, protein S, or AT deficiency), would benefit from taking an anticoagulant (in addition to or instead of antiplatelet therapy) is not known. This, along with the lack of high-quality evidence that these inherited thrombophilias are linked to arterial thrombosis, leads many clinicians to avoid searching for inherited thrombophilia in patients with arterial events.

Pediatric considerations

Non-CNS arterial thrombosis in children within tertiary pediatric hospitals occurs with slightly less frequency than venous thrombosis. Arterial thrombosis in children is predominantly iatrogenic, related to vascular access (arterial puncture or catheter placement). Femoral artery thrombosis following cardiac catheter; peripheral artery thrombosis following arterial line placement, especially in neonates; and umbilical artery thrombosis (also in neonates) are the most common clinical situations encountered. Thrombosis in arteries of transplanted solid organs is another significant clinical entity. Spontaneous arterial thrombosis (including the aorta) can occur but is rare. Coronary artery thromboses are almost always in the setting of giant aneurysms secondary to Kawasaki disease. Peripheral artery disease classically seen in vasculopathic adults is almost never seen in children.

The degree of tissue ischemia depends upon the degree of occlusion and the presence or absence of a collateral circulation. Immediate removal of the catheter may restore blood flow and relieve distal ischemia, especially as any coexistent arterial spasm resolves over subsequent minutes to hours. Anticoagulation, thrombolysis, and surgical thrombectomy are all reported as appropriate therapies depending on the degree of ischemia, and the requirement for future vascular access for therapeutic procedures (eg, cardiac catheters). Initial anticoagulation with heparinoid is often adequate therapy. The optimal duration of anticoagulation therapy, and the role of subsequent platelet inhibition therapy, remain unknown. True rates of long-term consequences such as claudication or limb length discrepancy (resulting from growth failure) remain unknown.

Atrial fibrillation and stroke prevention

For most patients with nonvalvular atrial fibrillation, the risk of bleeding with anticoagulation using either a DOAC or a VKA is outweighed by the benefit. Readers should refer to the latest AHA guidelines for details.

Neonatal stroke

Neonatal stroke, defined as a cerebrovascular event that occurs between 28 weeks gestation and 7 days of age, occurs in 1 in 250 live births. There is a male predominance. Approximately 60% present with early symptoms, mostly seizures and nonfocal neurological signs during the first 3 days of life. The seizures are often focal in nature. About 40% of affected children do not have specific symptoms in the neonatal period and are only recognized later with the emergence of motor impairment, developmental delay, specific cognitive deficiency, or seizures. It is often difficult to determine whether the stroke occurred in utero, at the time of delivery, or within the first week. Most neonatal stroke occurs in the distribution of the left-middle cerebral artery. MRI and angiography are the best tests to determine extent of disease. The mechanism of stroke in the different groups of newborns with stroke (term versus preterm; symptomatic neonates versus those with a delayed presentation; sick versus well) is likely to be different. Risk factors include congenital heart disease or so-called TORCH (toxoplasmosis, syphilis, herpes, cytomegalovirus) infections, systemic bacterial infections, or metabolic diseases. Recent studies have shown there is no association with inherited thrombophilia and therefore

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Table 9-2 "Unexplained" arterial thromboembolism: suggested approach to structured evaluation

A. Is arteriosclerosis the underlying problem?
Arteriosclerotic changes demonstrated on imaging studies or pathology specimens?
Arteriosclerosis risk factors present?
Cigarette smoking
High blood pressure
High low-density lipoprotein (LDL) cholesterol
Low high-density lipoprotein (HDL) cholesterol
High lipoprotein(a)
Diabetes mellitus
Obesity
Family history of arterial problems in young relatives (<50 years old)
Prior thoracic irradiation
B. Has the heart been thoroughly evaluated as an embolic source?
Atrial fibrillation—EKG, Holter, or event monitor
Patent foramen ovale—obtain cardiac echo: transthoracic echo with bubble study and Valsalva maneuver; if negative, consider transesophageal echo with bubble study
C. Other causes
Is the patient on estrogen therapy (contraceptive pill, ring, or patch; hormone replacement therapy)?
Does the patient use amphetamines, cocaine, or anabolic steroids?
Is there evidence for Buerger's disease (does patient smoke tobacco or cannabis)?
Does patient have symptoms suggestive of a vasospastic disorder (Raynaud's)?
Were anatomic abnormalities seen in artery leading to the ischemic area (web, fibromuscular dysplasia, dissection, vasculitis, external compression)?
Does patient have evidence of a rheumatologic or autoimmune disease (arthritis, purpura, or vasculitis)? Consider laboratory workup for vasculitis and immune disorder.
Is there a suggestion of an infectious arteritis?
Could the patient have hyperviscosity or cryoglobulins?
D. Thrombophilia workup for arterial events
Hemoglobin and platelet count (PVT and ET are also associated with increased arterial thrombotic events)
Antiphospholipid antibodies
Anticardiolipin IgG and IgM antibodies
Anti–β2-glycoprotein I IgG and IgM antibodies
Lupus anticoagulant
Flow cytometry to exclude PNH (if any evidence of hemolysis or cytopenias are present)
Do *not* test for MTHFR polymorphisms, PAI-1 or tPA levels or polymorphisms, fibrinogen, or factor VIII activities
Suggest *not* to test for FVL mutation, prothrombin gene mutation, protein C/S activity and antithrombin activity as relationship is not established
Suggest *not* to do homocysteine testing without other clinical signs as it will frequently reveal modest elevations of unknown clinical significance. Arterial thrombosis is more commonly associated with very marked elevations as seen with hyperhomocysteinuria

EKG, electrocardiogram; MTHFR, Methylenetetrahydrofolate reductase; PAI-1, plasminogen activator inhibitor 1.

*Uncertain clinical utility.

testing for this is of no benefit. Recurrence rates for most perinatal/neonatal arterial ischemic stroke are extremely low, and hence there is no justification for anticoagulant or antiplatelet therapy once the diagnosis is made. In cases of cardioembolic stroke (with proven embolic source remaining in the heart), or traumatic major vessel

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dissection, then anticoagulation or antiplatelet therapy is usually warranted. Neonatal supportive care remains the mainstay for all infants, including managing seizures, glucose, and blood pressure and preventing infection. Fifty percent of infants with perinatal events are neurologically normal by 12 to 18 months of age. Long-term sequelae such as mild hemiparesis, speech or learning problems, behavioral problems, and seizures are more likely to persist in patients who present outside the newborn period. There is no specific evidence that early rehabilitation therapy improves long-term outcome, but it is a very reasonable extrapolation given the role of early intervention in improving the neurological outcome for many other infants who suffer neurological insults in early life. The recurrence risk for subsequent pregnancies appears to be low in most cases.

Childhood stroke

Stroke is the most common cause of brain attack (focal neurological deficit) symptoms in adults, accounting for approximately 3/4 of cases in patients presenting to the emergency department. In contrast, there is a much lower a priori probability of stroke in children presenting with brain attack symptoms. Migraine is the most common cause of sudden onset focal neurological symptoms and signs, first febrile or afebrile seizures are the second most common diagnosis, and then Bell's palsy, before ischemic or hemorrhagic stroke and conversion disorders. Thus, less than 10% of children who present to an emergency department with acute focal neurological symptoms and signs have stroke. More common presenting features of stroke include hemiparesis (22% to 100%), headache (16% to 45%), altered mental state (12% to 24%), speech disturbance (28% to 55%), altered consciousness (24% to 52%), and seizures (11% to 58%). Age influences the clinical presentation, with seizures, altered mental state, and nonfocal signs being more likely in infants. History should include any evidence of recent head/neck injury or neck manipulation, varicella infection in the last 6 to 12 months, history or family history of migraine, and oral contraceptive pills or illicit drug use in adolescents. The nonspecific symptoms and alternative potential diagnoses often lead to delay in diagnosis of childhood stroke, with multiple studies reporting the average time from symptom onset to diagnosis as being in excess of 20 hours. This obviously has massive consequences in terms of the use of acute therapies such as thrombolysis or endovascular procedures.

Arteriopathies (vasculopathies) are the most common cause of arterial ischemic stroke in children, accounting for about 50% of cases. Cardioembolic strokes frequently occur in children with underlying congenital heart disease and most often around the time of major surgical procedures. These may be in the anterior or posterior cerebral circulations and are usually single events, although occasionally showers of embolic lesions can be seen on neuroimaging. The risk of recurrence usually relates to the flow abnormalities within the heart, the presence or absence of further source clot, and the effectiveness of anticoagulation. Dissection of major vessels, including the extracranial carotid artery or the vertebral basilar system, is not uncommon after minor trauma or twisting forces. Often formal angiography is required to exclude or confirm the diagnosis. Most protocols for initial imaging of pediatric stroke patients include extension of the vascular imaging to include the neck vessels to consider this potential diagnosis.

The role of thrombophilias in the etiology of pediatric stroke remains controversial. While many studies report associations between stroke and heterozygous thrombophilic states in children, the methodology of most studies is less than ideal, and the evidence that links the blood results to recurrence or outcome, and hence impacts on potential therapy, is weak.

A significant proportion of childhood strokes are truly cryptogenic, occurring in otherwise well children without any precipitating factors. Multiple other associations have been suggested, including iron deficiency; however, many events remain unexplained. Fortunately, in these cases the recurrence risk appears to be lower, but it is difficult to be totally reassuring to patients and their families. Stroke is very common in children with underlying sickle cell disease (see Chapter 7).

Anticoagulation (LMWH, UFH, warfarin) or antiplatelet (predominantly aspirin) therapy is aimed at reducing the risk of recurrence and maximizing the recovery of the ischemic penumbra surrounding the infarcted area. The evidence supporting any specific approach is relatively low, and the risk of increasing secondary hemorrhage must always be considered. In general, arteriopathies are thought to require antiplatelet therapy, while cardioembolic and dissection-related strokes are thought to require anticoagulation. The question of whether at presentation, anticoagulation therapy should be commenced with conversion to antiplatelet therapy once cardioembolic causes or dissection have been excluded—or alternatively, whether antiplatelet therapy should be commenced with conversion to anticoagulation once cardioembolic causes or dissection have been proven—remains unanswered. There are clear geographic differences in approach. The optimal duration of these therapies is unclear, but anticoagulation is frequently used for 3 months, while antiplatelet therapy is often prescribed for 12 months post stroke.

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Table 9-3 Prevalence of thrombophilia and relative risk estimates for various clinical manifestations

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden mutation (heterozygote)	Prothrombin 20210A mutation (heterozygote)
Prevalence in the general population	0.02%	0.2%	0.03%-0.13%	3%-7%	0.7%-4%
Relative risk for a first venous thrombosis	5-10	4-6.5	1-10	3-5	2-3
Relative risk for recurrent venous thrombosis	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3

As many as 65% of affected children develop lifelong disabilities, such as neurological defects and seizures, and the risk of a second stroke is 20%. Despite therapy, mortality rates as high as 10% have been reported.

Thrombophilias

The terms *thrombophilia* and *hypercoagulable state* refer to hereditary or acquired predispositions to develop thrombosis. Although the clinical relevance of testing for these conditions has diminished somewhat in recent years, the hematologist must be familiar with the nature, limitations, and interpretation of such testing (Table 9-3). It is important to note that first-degree relatives of patients who have experienced VTE (provoked less so than unprovoked) are at an increased risk of venous thrombosis, irrespective of thrombophilia test results. Table 9-4 lists the prevalence and association with various clinical manifestations.

Inherited thrombophilias

Family history of VTE

Having a first-degree relative with a history of VTE increases an individual's risk of VTE 2- to 4-fold. Young age of incident VTE, and/or an unprovoked clot in the affected relative, and having more than 1 affected first-degree relative all increase the likelihood of developing a first VTE. Whether a strong family history of VTE is a risk factor for *recurrent* VTE, and thus should be used in decision-making on length of anticoagulation therapy after a first episode of VTE, is not known.

Table 9-4 Estimated number of asymptomatic thrombophilic women or women with a positive family history for VTE who would have to avoid using oral contraceptives to prevent 1 VTE, and estimated number needed to test

Thrombophilia	Risk on OC per year, %	Risk difference per 100 women	N not taking OC to prevent 1 VTE	N of female relatives to be tested
Antithrombin, protein C, or protein S deficiency				
Deficient relatives	4.3	3.6	28	56
Nondeficient relatives	0.7			
Factor V Leiden or prothrombin 20210A mutation				
Relatives with the mutation	0.5	0.3	333	666
Relatives without the mutation	0.2			
Family history of VTE				
General population, no family history	0.04†	0.03	3333	None
General population, positive family history	0.08†	0.06	1667	None

OC, oral contraceptive.

†Based on a population baseline risk of VTE in young women of 0.01% per year, a relative risk of VTE by use oral contraceptives of 4, and a relative risk of 2 of VTE attributable to positive family history.

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Factor V Leiden

The prevalence of heterozygous factor V Leiden (FVL) is 3% to 8% in populations of European origin and 1.2% in African Americans. It rarely is found in native African and Asian populations. Homozygous FVL occurs in 1 in 500 to 1600 people of European origins.

Prothrombin 20210 mutation

The mutation is found most commonly in individuals of Southern European ancestry, with a prevalence throughout Europe of 0.7% to 4%. In the United States, it occurs in 2% of the general population and in 0.5% of the African American population. The prothrombin 20210 mutation is rare in other populations of non-European origin. Homozygosity for the prothrombin 20210 mutations occurs, by calculation, in approximately 1 in 4000 individuals of European heritage.

Protein C deficiency

The prevalence of inherited protein C deficiency in the general population is approximately 1 in 500 to 600. By calculation, homozygous or double heterozygous protein C deficiency occurs in approximately 1 in 1 million individuals.

Protein S deficiency

Reported prevalence in the general population varies between 1 in 800 and 1 in 3000, but because of difficulties in establishing the normal range of protein S concentrations and in making an accurate diagnosis, the true prevalence of protein S deficiency is not known (Table 9-4).

Antithrombin deficiency

Inherited AT deficiency occurs in 1 in 500 to 5000 people. Deficiencies are typically heterozygous, as homozygous deficiencies are almost always incompatible with life.

Acquired hypercoagulable states

Estrogen exposure

Estrogen exposure, whether related to pregnancy, hormonal contraceptives, postmenopausal hormone replacement therapy or gender-affirming treatment, is perhaps the most common acquired hypercoagulable state. The precise mechanism by which estrogen increases the risk for thrombosis is incompletely understood, but increased levels of procoagulant factors such as factors II, VII, VIII, and X likely play a role. Increased risk of thrombosis begins shortly after initiation of estrogen therapy and continues for up to 3 months after discontinuation. See Chapter 3 for additional details about the risks associated with hormonal contraceptives and pregnancy.

There are a few unique features to the management of estrogen-related thrombosis. While the risk of recurrence in the absence of continued estrogen exposure or other risk factors is remarkably low, removing or avoiding estrogen exposure is not always desired or possible. However, in other situations, such as women who require hormonal therapy for management of heavy menstrual bleeding or transgender women using hormonal therapy, the risks of discontinuing estrogen may outweigh the benefits in an anticoagulated patient. The data on safety of continuing estrogen in the presence of therapeutic anticoagulation are unfortunately sparse although post hoc analysis of data from registry trials of rivaroxaban demonstrated no increased risk of recurrent VTE in women receiving hormonal therapy on therapeutic anticoagulation. The decision to continue estrogen therapy, including the duration of that therapy and the expected requirement that anticoagulation would continue during and beyond that timeframe, warrants a careful discussion of risks and benefits.

Cancer

Approximately 20% of all VTEs occur in patients with cancer. About 5% of patients with unprovoked VTE have a previously undiagnosed cancer at the time of the VTE, and another 10% of patients with unprovoked VTE will be diagnosed with a cancer in the year following the VTE diagnosis. Evaluation for occult cancer should be considered in selected patients, such as those with recent weight loss and other unexplained symptoms or abnormalities on routine laboratory testing, such as anemia. Patients presenting with unprovoked VTE who are not up-to-date on age- and gender-appropriate cancer screening (eg, colorectal cancer screening, mammography, pap testing) should be encouraged to become so. Recent studies show that extensive screening (eg, computed tomography of the chest/abdomen/pelvis, or PET/CT) for cancer in all patients with unprovoked VTE does not result in decreased cancer-associated morbidity or improved survival. Similar to adults, children with cancer are at increased risk for the development of VTE, but the majority of these VTEs are related to central venous catheters or cancer therapy, such as asparaginase or high-dose corticosteroids.

Based on superior efficacy in several randomized comparisons with warfarin, LMWH is the standard of care for cancer-associated VTE. Randomized studies that compared edoxaban or rivaroxaban to LMWH for the treatment of cancer-associated thrombosis showed the DOACs to be noninferior to LMWH for the composite endpoint of recurrent VTE and major bleeding. In both studies,

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there appeared to be a relative increase in gastrointestinal bleeding with the DOAC. Studies comparing apixaban to LMWH in this same population also showed noninferiority with respect to recurrent VTE and no difference in rates of major bleeding, including gastrointestinal bleeding. Overall, DOACs appear to be a reasonable alternative to LMWH for the treatment of CAT, and the choice for an individual patient should be made considering potential drug interactions, organ function, risk of bleeding, cost, and patient preference.

Myeloproliferative disorders

ET and polycythemia vera are associated with a substantial risk for thrombosis (arterial more commonly than venous). A gain-of-function mutation of the Janus kinase-2 (JAK2) enzyme, the *JAK2* V617F mutation, is found in nearly 100% of patients with polycythemia vera and in 50% of those with ET, and is associated with an increased risk of thrombosis, either arterial or venous, in patients with ET, and may be somewhat dependent on variant allele frequency. At present, however, there are no data to suggest that therapeutic anticoagulation decisions should be based on the presence or absence of the mutation. These disorders are discussed in more detail in Chapter 17.

Paroxysmal nocturnal hemoglobinuria

PNH is a clonal hematopoietic stem cell disorder resulting from an acquired mutation of the phosphatidylinositolglycan class A gene, leading to absent or decreased cell surface expression of glycoprotein (GP) I–anchored proteins on the surface of blood cells. PNH is associated with increased risk of venous and arterial thrombosis, which most often occurs in intra-abdominal veins, particularly the hepatic veins (Budd-Chiari syndrome). Cerebral and peripheral vein thromboses also occur, but less commonly. The pathophysiology of thrombosis is not well-understood, and no consistent abnormalities have been found.

Screening for PNH by Fluorescein-labeled proaerolysin (FLAER) by peripheral blood flow cytometry or alternatively CD55 and CD59 is warranted in thrombophilia evaluations of patients with venous or arterial thrombosis plus unexplained hemolysis or peripheral blood cytopenias. Antithrombotic therapy can be used for the treatment and secondary prevention of PNH-associated thrombosis, but "breakthrough" clotting events are well-described. Long-term treatment with the complement inhibitor eculizumab reduces the risk of thromboembolism (and improves life expectancy) in patients with PNH.

Antiphospholipid antibodies

APLAs are acquired autoantibodies directed against phospholipids and phospholipid-binding proteins, such as β_2-glycoprotein I and prothrombin. They are associated with arterial thromboembolism, VTE, and pregnancy complications. The precise pathophysiologic explanation for the clinical phenomena is not known. Diagnosis of APS requires objectively documented venous or arterial thrombosis, unexplained recurrent (3 or more) early (<10 weeks of gestation) miscarriages or 1 or more late pregnancy losses, or pregnancy complications associated with placental insufficiency together with persistent laboratory evidence of APLAs, tested at least 12 weeks apart. The syndrome can occur either as primary APS (not associated with any other diseases) or secondary APS (associated with autoimmune diseases, malignancy, or drugs). Importantly, based on the definition of the syndrome, the clinical variation in phenotype is large, with some patients experiencing all manifestations of APS, whereas the same diagnosis is made in patients with, for example, a provoked VTE and 2 consecutive positive test results. From this it follows that the prognosis and inferences about prognosis cannot be easily generalized to all patients who have a diagnosis of APS.

Prevalence

The prevalence of APS is poorly defined, but APLAs are found in nearly 50% of patients with systemic lupus erythematosus and up to 5% of the general population. Nearly 40% of patients with systemic lupus erythematosus meet diagnostic criteria for APS.

Testing

Laboratory evidence of an APLA is defined as: (1) moderately or highly positive (>40 GPL or MPL [where Antibodies to IgM and IgG are reported in MPL (IgM Phospholipid Units, Note: 1 MPL unit is 1 microgram of IgM antibody) or GPL (IgG Phospholipid Units, Note: 1 GPL unit is 1 microgram of IgG antibody)], or above the 99th percentile of a laboratory's own reference population) immunoglobulin G (IgG) or immunoglobulin M (IgM) anti-β_2-glycoprotein I antibodies, (2) moderately or highly positive IgG and IgM anticardiolipin antibodies, or (3) evidence of a lupus anticoagulant (sometime called a lupus inhibitor). Lupus anticoagulants are detected when phospholipid-dependent clotting times (eg, aPTT, Russell viper venom time) are prolonged. False positive lupus anticoagulant test results are not uncommon, occurring frequently in patients who are on oral anticoagulants. False negative results may occur if the blood sample was suboptimally centrifuged and the prepared plasma was not platelet poor. DOACs can variably cause false positive and

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false negative results, although new methods of absorbing the DOAC to enable accurate testing are currently being evaluated. Because APLA can be transient, guidelines suggest that repeatedly positive tests (at least 12 weeks apart) be documented, along with corresponding clinical phenomena, to confirm a diagnosis of APS.

A number of other APLA tests are not part of the revised Sapporo criteria, as their association with thrombosis or pregnancy loss has not been established, including immunoglobulin A (IgA) anticardiolipin and IgA anti—β_2-glycoprotein I antibodies, antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, and antiphosphatidylinositol antibodies. There is presently no clear indication for testing for these additional APLAs in routine clinical practice. Familiarity with the methods of a particular laboratory is especially desirable for APLA testing.

The INR determined from plasma is occasionally invalid in APS patients on VKAs because of a lupus anticoagulant effect on the prothrombin time. Furthermore, for patients with APLAs, INR determinations by point-of-care INR monitors are often inaccurate and significantly overestimate a patient's level of anticoagulation, thereby putting the patient at risk of recurrent thrombosis. Alternative tests, such as chromogenic factor X activity, can be used to measure the VKA effect when laboratory-based or point-of-care INR testing may be inaccurate. The target ranges for these tests depend on the reagents and instruments used for their determination, but an INR range of 2.0 to 3.0 typically corresponds to a chromogenic factor X activity of approximately 20% to 40%.

Risk for thrombosis

Positivity for all 3 APLA tests (ie, lupus anticoagulant, anticardiolipin, and anti–β_2-glycoprotein I antibody tests; so-called triple positive) is associated with the highest risk for both venous and arterial thrombosis (and pregnancy loss). Patients with APS are thought to be at high risk of recurrent thrombosis, but the degree to which the recurrence risk is increased (compared to a similar patient who tests negative for APLA) is not well established. There is a 5% to 15% failure rate of warfarin therapy in preventing recurrent thrombosis in patients with APS.

Management

Because of the previously mentioned challenges related to laboratory APLA testing and interpretation, as well as the transient nature of antibodies in many patients, it is advisable to always question a diagnosis of APS until the previous laboratory test results have been reviewed and, if necessary, repeat testing has been performed. Because of the high rate of recurrent VTE, patients with APS with a history of unprovoked VTE should be maintained on anticoagulation indefinitely. Randomized trials have shown that a target INR range of 2.0 to 3.0 is equally effective in preventing recurrent thrombosis as a target range of 3.0 to 4.0. If the aPTT is prolonged at baseline because of a lupus anticoagulant, then anti–factor Xa levels need to be used to monitor heparin therapy. If the Prothrombin time (PT) is prolonged at baseline, then the validity of the patient's INR should be checked once the patient is on VKA by comparing the INR to a chromogenic factor X assay. It then can be determined whether the INR is a reliable measure of that patient's anticoagulation and can be used for VKA monitoring. As APLA titers can fluctuate over time, a recorrelation between the INR measured by point of care and from a phlebotomy plasma sample should be performed every so often, such as every 4 to 6 months. It is not known, however, what the optimal frequency of such recorrelation is. The role of DOACs in the treatment of patients with APS remains uncertain. A trial of rivaroxaban compared to warfarin for the prevention of VTE in patients with triple positive APS was ended early because of a striking excess of thrombotic events in subjects treated with rivaroxaban. Specific data on lower-risk (ie, not triple positive) groups are lacking, but a trial including a more generalized group of patients with thrombotic APS demonstrated a numeric increase in recurrent thrombosis in the rivaroxaban group, although not reaching statistical significance. Of note, breakthrough events appear to be primarily arterial rather than venous. In general DOACs should be avoided in favor of warfarin in high-risk patients (triple positive, history of arterial events) and should be considered only with caution and careful risk-benefit discussion in lower-risk patients.

It is not known whether patients with arterial thrombosis and APS are more effectively treated with antiplatelet or VKA anticoagulation therapy. Some evidence, from patients with APLA and noncardioembolic stroke, suggests that aspirin and VKA therapy may be equally effective. In the absence of prospective randomized trial data, this clinical question remains unanswered. Rituximab has been shown to decrease APLA titers in some patients, but whether lowering (or spontaneous disappearance) of APLA leads to a decreased thrombosis risk is not known. The management of pregnant women with APLA is discussed elsewhere in this self-assessment program.

Thrombophilia in children

The rationale for thrombophilia testing in children in terms of outcomes or alterations to duration or intensity of treatment remains dubious. Thrombophilia testing

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is frequently performed because clinicians, in an attempt to provide some answers for desperate parents, embark on testing without understanding that the interpretation of any positive results is fraught with uncertainty. Alternatively, testing is often driven by parents who have been scouring the internet for answers and come asking about thrombophilia. At present, consensus recommendations suggest that thrombophilia testing (AT, protein C, protein S, factor V Leiden, prothrombin gene mutation, and lupus anticoagulant/APLAs) may be appropriate in children with unprovoked and recurrent VTE. Some reports suggest that anatomical abnormalities (eg, absent IVC, thoracic outlet syndrome) are more likely to be the cause of spontaneous VTE in children and adolescents than a plasma-derived thrombophilia, and that careful imaging is required. There seems to be no role for thrombophilia testing in neonates, infants, and children with provoked VTE, especially asymptomatic or symptomatic central line–related VTE. The role of testing nonsymptomatic siblings and further first-degree family members in high-risk families with known AT, protein C, or protein S deficiency carriers, and in individuals with a first-degree family history of unprovoked young-onset VTE is uncertain, but it would seem that adolescents, especially females, have the most to gain from such testing because this might inform use of oral contraceptive agents and potential thromboprophylaxis in pregnancy and postpartum.

APLA can be found in a high percentage of children without any underlying disorder, with an estimated frequency that ranges from 3% to 28% for anticardiolipin antibodies and from 3% to 7% for anti-β_2-GPI antibodies. The majority of these antibodies are transient, presumably post viral, and disappear within a few weeks to few months (~3 to 6 months). Studies of healthy children who present for surgery, especially tonsillectomy, show a 2% prevalence of transient lupus anticoagulant with no apparent pathologic consequence because of the fact that these postinfectious APLAs more commonly bind cardiolipin in a non-β2-glycoprotein-I–dependent manner. The prognostic significance of the transient lupus anticoagulant in children who present with thrombosis in the setting of concurrent infection is probably similar to that of children who have an asymptomatic lupus anticoagulant. Transplacental transmission of maternal APLA has been reported in the newborn period. Registry data suggest that these antibodies are not associated with thromboembolic events.

There are a number of other acquired thrombophilic states in children. Acquired AT deficiency secondary to asparaginase chemotherapy or nephrotic syndrome has been implicated in the pathogenesis of increased thrombosis in these patients; however, AT supplements have not been shown to be beneficial. In recent years, administration of AT has become popular in children requiring UFH therapy, especially those on extracorporeal membrane oxygenation (ECMO). This is predicated on the untested theory that because many sick children have acquired AT deficiency (and young infants have naturally lower AT levels), providing more substrate for heparin to bind facilitates a reduction in heparin requirements and more effective anticoagulation. In most cases, this therapy involves increasing AT to significant supraphysiological levels for the individual child. Data supporting this practice are sparse. The reduction in heparin requirements following AT administration is highly variable and studies of children on ECMO have thus far either not examined or not shown any beneficial effect of AT on clinical outcomes, including bleeding, blood product administration, ECMO circuit changes, length of stay, or mortality. Further, AT is used to assist achievement of therapeutic target ranges for UFH (whether using activated clotting time, aPTT or anti-Xa factor as the monitoring test) that in fact have never been proven to be optimal in any comparative trial. In other groups of hospitalized children, such as those in the neonatal intensive care unit or the general ward, AT administration may be either ineffective or harmful.

A large analysis of AT administration in children on ECMO reported 8972 children who received ECMO in 43 hospitals across the United States over a decade, 1931 (21.5%) of whom had received at least 1 dose of AT during their ECMO run (predominantly early in the ECMO course). AT use varied between hospitals from 0% to 80% but increased over the course of the study, from approximately 2% in 2005 to 50% by 2012. The children who received AT were more likely to be younger, smaller, and have chronic conditions. AT administration was associated with a higher incidence of thrombosis (OR 1.55; 95% CI, 1.36 to 1.77), including pulmonary embolus and ischemic stroke, and a higher incidence of hemorrhage (OR 1.27; 95% CI, 1.14 to 1.42), including central nervous system hemorrhage. There was no difference in mortality. Routine use of AT supplementation in children requiring UFH for ECMO or any other reason is difficult to justify.

In general, the rates of thrombosis in children with cancer are much lower than those seen in adults, vary according to cancer type, and are associated with CVADs or direct venous compression. Myeloproliferative diseases and PNH are rare in children, but if they do occur, can be associated with thrombosis.

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Table 9-5 Reasons for and against thrombophilia testing

Reasons for testing
Patient with thrombosis
Influence on duration of anticoagulation therapy
Possible explanation (for patient and physician) why thrombosis occurred
Reasons against testing
Lack of therapeutic consequences even if test positive/abnormal
Suboptimal performance of tests (false positive and false negative results) or misinterpretation of tests
Poor medical advice based on test results
Anxiety if test is positive
False sense of security that thrombosis risk is low if test result normal/negative
Cost of testing
Lack of impact for asymptomatic first-degree relatives (possible exception is women contemplating estrogen use or pregnancy)
Impact on ability to obtain life or health insurance

Interpreting test results and educating patients

Reasons to test or not to test are outlined in Table 9-5. When interpreting thrombophilia laboratory test results, it is important to be aware of the circumstances that lead to abnormal test results without a true thrombophilia being present. When a thrombophilia is identified, educating the patient and the patient's family members is important. Online education and support resources on a variety of thrombophilias and the genetic aspects of family testing exist (eg, see http://www.clotconnect.org or http://www.stoptheclot.org).

Antithrombotic drugs

Anticoagulants

Heparins

Mechanism of action

LMWHs inactivate mostly factor Xa, whereas UFH acts against thrombin and factor Xa. Fondaparinux is a synthetic pentasaccharide that binds to AT, leading to specific inactivation of factor Xa.

Unfractionated heparin

UFH at therapeutic doses is given through continuous intravenous infusion and is typically monitored using aPTT. The therapeutic aPTT range depends on the heparin sensitivity of the aPTT reagent and the instrument used by a laboratory. A therapeutic aPTT is considered that which corresponds to a plasma anti-Xa heparin level of 0.3 to 0.7 U/mL. Optimally, a coagulation laboratory should provide clinicians with the therapeutic aPTT range for the reagent-instrument combination used in that laboratory.

UFH therapy also can be monitored with anti-Xa levels, and a number of laboratories have switched to routinely using this method for UFH monitoring. Although this is an acceptable alternative, it is not known which method leads to superior safety or efficacy of heparin therapy. UFH is mostly cleared by the reticuloendothelial system and to a smaller degree by the kidney. The half-life of heparin in plasma depends on the dose given. It is 60 minutes with a 100 U/kg bolus. A patient on continuous infusion intravenous UFH at therapeutic doses likely will have a return to the baseline aPTT within 3 to 4 hours after discontinuation of heparin.

Weight-based heparin-dosing nomograms achieve therapeutic aPTTs faster than other approaches to selecting a UFH dose. In many patients at average risk for bleeding, a loading dose of 80 U/kg of intravenous heparin, followed by a continuous infusion of 18 U/kg/h is appropriate for full anticoagulation. This dosing, however, may have to be modified in the patient at higher risk for bleeding. The aPTT or anti-Xa level should be determined 6 hours after initiation of heparin and each dose change, and once every 24 hours once the aPTT or anti-Xa level is in the therapeutic range. Long-term use of UFH leads to an increased risk of osteoporosis and carries a risk for heparin-associated thrombocytopenia.

UFH remains a commonly used anticoagulant in pediatric patients. There are a number of specific factors that may alter the effect of UFH in children (Table 9-6). The clinical implications of these changes on dosing, monitoring, and the effectiveness/safety profile of UFH in children remains uncertain.

There have been no reported clinical outcome studies to determine the therapeutic range for UFH in neonates or children, so the therapeutic range for all indications is extrapolated from those used in VTE therapy in adults. There are multiple reasons why this extrapolation might be invalid; however, the safety and efficacy of this approach, in experienced hands, seem reasonable.

Bolus doses of 75 to 100 U/kg result in therapeutic aPTT values in 90% of children at 4 to 6 hours post bolus. Maintenance UFH doses are age dependent, with infants (up to 2 months) having the highest requirements (average 28 U/kg/h) and children over 1 year having lower requirements (average 20 U/kg/h). The doses of UFH required for older children are similar to the weight-adjusted

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Table 9-6 Factors in children that affect the action of UFH

UFH factor	Age-related difference
UFH acts via AT-mediated catabolism of thrombin and factor Xa	Reduced levels of AT and prothrombin
	Reduced capacity to generate thrombin
	Age-related difference in anti-Xa: anti-IIa activity of UFH
UFH is bound to plasma proteins, which limits free active UFH	Alterations in plasma binding
Endothelial release of TFPI	Age-related differences in amount of TFPI release for same amount of UFH

TFPI, tissue factor pathway inhibitor.

requirements in adults (18 U/kg/h). However, boluses of 75 to 100 U/kg in children have been shown to result in excessive prolongation of aPTT for over 100 minutes, implying that the recommendations may need to be reexamined. In many cases, especially where bleeding risk is higher, therapy should be commenced with an infusion only, and no boluses. Reduced doses are usually required in renal insufficiency.

The ratio of anti-Xa to IIa effect changes with age and dose, and the half-life or UFH also varies with age. There are no published studies in children that establish the ideal frequency of UFH monitoring, and vascular access is a frequent limiting factor.

Probably the most common cause of fatal bleeding secondary to UFH relates to accidental overdose, especially in neonates. While rarely reported in the medical literature, the number of deaths reported in the popular press appears to be increasing. This often occurs in children who are receiving low-dose UFH flushing of vascular access devices, intended for example to be 50 U/5 ml UFH. Errors in vial selection and failure of bedside checking procedures result in 5000 U/5 ml UFH being injected, and in small infants this results in a massive and unexpected overdose of UFH. Wards should actively manage the choices of UFH preparations available to their staff to minimize the risk of confusion. Staff should be educated in the dangers of UFH and encouraged to be vigilant at all times when administering this drug, which consistently ranks in hospital lists of the medications most commonly involved in medication errors.

Low-molecular-weight heparin

The various LMWH drugs differ in their composition, and thus in their degree of inhibition of thrombin and factor Xa. Therefore, dose recommendations for VTE prophylaxis and for full-dose treatment vary for the various LMWHs. The lack of significant binding of LMWHs to plasma proteins gives them a more predictable anticoagulant effect than UFH, so that fixed or weight-adjusted dosing is possible without the need for routine anticoagulant laboratory monitoring. The peak plasma effect is reached 3 to 4 hours after injection. The half-lives of the various agents differ, ranging between 3 and 7 hours. Once- or twice-daily dosing regimens are available for the different drugs. Since the LMWHs are—to varying degrees—renally cleared, anti-Xa activity measurement at steady state is suggested in patients with renal impairment. Below a glomerular filtration rate of 30 mL/min, caution with LMWH dosing is appropriate and reference to the package insert for the individual LMWH being used appears advisable to determine dose. In severe renal impairment (creatinine clearance < 15 mL/min) and dialysis dependence, UFH should be chosen over LMWH. It may be appropriate to increase the prophylactic dose of LMWH for patients with morbid obesity (body mass index of > 35 kg/m^2). For full-dose LMWH use, dosing should be based on actual body weight, and anti-Xa measurement generally is not necessary for patients weighing up to 150 kg. Anti-Xa activity measurement and twice- (rather than once-) daily dosing should be considered in patients with morbid obesity.

An expected anti-Xa level (obtained 3 to 4 hours after subcutaneous injection) is in the order of 1.0 to 2.0 U/mL for once-daily dosing; for twice-daily dosing, it is 0.6 to 1.2 U/mL.

LMWH has become the anticoagulant of choice in many pediatric patients for a variety of reasons. However, the predictability of the anticoagulant effect with weight-adjusted doses is lower than in adults, presumably because of differences in binding to plasma proteins. Table 9-7 provides guidance for dosing in children according to age. Most clinical data for LMWH in pediatric patients used enoxaparin, although dalteparin has recently become the only LMWH approved by the FDA for use in children.

Therapeutic ranges for LMWH are extrapolated from results in adults and based on anti-Xa levels; the guideline for subcutaneous administration twice daily being 0.50 to 1.0 anti-Xa U/mL at 2 to 6 hours following injection.

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Table 9-7 Therapeutic and prophylactic dosing of enoxaparin, tinzaparin, and dalteparin in children according to age

Drug	Therapeutic dose	Prophylactic dose
Enoxaparin		
≤2 months of age	1.5 mg/kg SC b.d.	1.5 mg/kg SC o.d.
>2 months of age	1 mg/kg SC b.d.	1 mg/kg SC o.d.
Tinzaparin		
≤2 months of age	275 U/kg SC o.d.	75 U/kg SC o.d.
2-12 months of age	250 U/kg SC o.d.	75 U/kg SC o.d.
1-5 years	240 U/kg SC o.d.	75 U/kg SC o.d.
5-10 years	200 U/kg SC o.d.	75 U/kg SC o.d.
10-16 years	175 U/kg SC o.d.	50 U/kg SC o.d.
Dalteparin		
≤2 months of age	150 U/kg SC b.d.	150 U/kg SC o.d.
>2 months of age	100 U/kg SC b.d.	100 U/kg SC o.d.

b.d., twice daily; o.d., once daily; SC, subcutaneously.

Most studies in children have used this therapeutic range, although 1 study used a lower maximal level (0.8 U/mL) with good efficacy and safety outcomes. Once-daily regimens are described much less commonly, and intravenous use has also been reported, but rarely. Reduced doses are required in renal insufficiency.

Major bleeding rates with LMWH in children appear to be low in stable patients, and although reports vary from 0% to 19%, patient selection is critical; and in many cases of bleeding, titratable and more readily reversible UFH would have been a better therapeutic option (eg, immediate postoperative patients). There are no data on the frequency of osteoporosis (although case reports exist in extended use of LMWH, especially in premature infants), heparin-induced thrombocytopenia (HIT), or other hypersensitivity reactions in children exposed to LMWH. Temporary hair loss is reported.

Fondaparinux

Fondaparinux is specific against factor Xa and does not inhibit thrombin. It is given subcutaneously, reaches its peak plasma level in 2 hours, and because of a half-life of approximately 17 hours, it is dosed once daily. Because it does not bind significantly to plasma proteins, it can be given without laboratory monitoring as a fixed dose for prophylaxis of VTE or in body weight–adjusted fashion for therapy of VTE. It is cleared by the kidneys, and thus should not be used in patients with creatinine clearance < 30 mL/min. Fondaparinux does not cause (and is sometimes used to treat) HIT.

There are few data regarding fondaparinux in children. A single-arm, open-label, dose-finding, pharmacodynamic and safety study enrolled 24 patients aged 1 to 18 years and showed a dose of 0.1 mg/kg/d, mirroring the pharmacodynamic profile found in adults. Peak anti-Xa levels should be measured at 3 hours after infusion, targeting a level of 0.5 to 1 mg/L (units are expressed as a concentration, but this is a unit conversion from the anti-Xa assay). In addition, for patients requiring procedures that are receiving fondaparinux, procedures should be performed at least 24 hours after the last dose.

Management of bleeding

If bleeding occurs in a patient on UFH, intravenous protamine can be given, which binds to and neutralizes heparin. Protamine can impair platelet function and interact with coagulation factors, causing an anticoagulant effect of its own. Therefore, the minimal amount of protamine to neutralize heparin should be given. LMWH is only partially reversed by protamine. In case of significant bleeding on LMWH, however, protamine should be considered. Fresh frozen plasma likely has little, if any, effect on bleeding associated with heparin, LMWH, and fondaparinux and is not indicated unless there is also evidence of a coagulopathy resulting in factor depletion.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is a rare but important complication that can occur with both UFH as well as LMWH administration. It is discussed in detail in Chapter 11. The true rate of HIT in children appears greatly reduced compared to that in adults.

Thrombin inhibitors

This section discusses only *parenteral* thrombin inhibitors; dabigatran, an oral thrombin inhibitor, is discussed in the "Direct oral anticoagulants" section in this chapter.

Hirudins

Natural hirudin is a 65 amino acid direct thrombin inhibitor derived from the saliva of the leech *Hirudo medicinalis*. It does not require the presence of AT to exert its anticoagulant effect. Several derivatives and recombinant products have been developed. Desirudin is also a 65 amino acid recombinant hirudin, administered subcutaneously. Peak plasma levels are reached 1 to 3 hours after injection. It is metabolized primarily by the kidney, and dose reductions are needed in patients with moderate and severe renal impairment. It is FDA-approved for postsurgical VTE prophylaxis. Bivalirudin is a synthetic, 20 amino acid polypeptide that directly binds to and inhibits thrombin. It is given intravenously and has a half-life of 25 minutes. Dose adjustment for severe renal impairment is necessary. It is FDA-approved for use during percutaneous transluminal coronary angioplasty, including patients undergoing it who have HIT.

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Bivalirudin is increasingly used in ECMO and ventricular assist devices in children although there are no clear data to support it is advantageous over UFH.

Argatroban

Argatroban is a small synthetic molecule that binds to and inhibits thrombin at its catalytic site. It is given intravenously. Since it is metabolized in the liver, dose reductions are required in patients with impaired liver function. Being independent of renal function, it can be used in patients across the range of renal function. Its half-life is 40 to 50 minutes. The drug can be started without the need for an initial bolus. The dosing is adjusted to an aPTT of 1.5 to 3 times the initial baseline value (not to exceed 100 seconds). It is FDA-approved for the treatment of HIT.

Vitamin K antagonists

Mechanism of action

All coagulation factors are synthesized in the liver, although von Willebrand factor and factor VIII also are produced in extrahepatic sites. Factors II, VII, IX, X, protein C, and protein S need to be carboxylated in a final synthetic reaction to become biologically active. This step requires the presence of vitamin K. The half-lives of the vitamin K–dependent coagulation factors are 4 to 6 hours for factor VII, 24 hours for factor IX, 36 hours for factor X, 50 hours for factor II, 8 hours for protein C, and 30 hours for protein S. Because of the long half-lives of some of these factors, particularly factor II, the full antithrombotic effect of VKAs is not reached until several days after having started these drugs. Because protein C has a relatively short half-life and decreases early, its lowering renders the patient hypercoagulable during the first few treatment days, before factor II, with its longer half-life, decreases and protects the patient from thrombosis. Thus, VKAs may create a paradoxical prothrombotic state in the first 5 days, putting the patient at risk for coumarin-induced skin necrosis and progression of thrombosis, unless a parenteral anticoagulant is given overlapping with the VKA in these first few days. The parenteral anticoagulant should be given for at least 5 days; thereafter it can be stopped when the INR is > 2.0.

Monitoring and dose requirement

VKAs are monitored by prothrombin time, which is standardized between laboratories as an INR. Coumarin VKAs are metabolized by the cytochrome P450 enzyme complex, mostly the enzymes CYP2C9 and CYP1A2. Because of a high degree of interindividual variability in the activity of these enzymes, there is a high degree of variability in the daily drug dose that patients need to maintain their INR in the narrow therapeutic range. Polymorphisms in the genes transcribing enzymes involved in the metabolism of VKAs, such as *CYP2C9* (cytochrome P2C9 enzyme) and *VKORC1* (vitamin K epoxide reductase complex-1) contribute to the interindividual variability in dose requirements. Finger stick (point-of-care) whole-blood INR monitors are available and, up to an INR of 4.0, yield results comparable to plasma-based measurements performed on a laboratory-based instrument. INR home monitoring by appropriately selected patients is safe and effective and a good treatment option. In some patients with fluctuating INRs, daily supplementation with microdose oral vitamin K, such as 100 to 300 mg/d, has been shown to decrease INR fluctuations.

Available VKAs

Two classes of VKAs exist: coumarin derivates (warfarin, phenprocoumon, acenocoumarol, and tioclomarol), which are the most widely used VKAs; and the indandione derivatives (fluindione, anisindione, and phenindione), which are used in some countries outside the United States. The only FDA-approved VKAs are warfarin (approved in 1954) and anisindione (approved in 1957). Warfarin has a pharmacodynamic half-life of 1 to 2.5 days, with a mean of approximately 40 hours.

The typical loading dose of warfarin in the hospitalized patient is 5 mg daily on days 1 and 2, with subsequent dosing based on the INR measurement after the first 2 doses. In children, this equates to initial doses of 0.1 to 0.2 mg/kg. A frail or elderly patient, one who has been treated with prolonged antibiotics, has liver disease, or has undergone intestinal resection, needs a lower dose in the first few days. Women generally need lower doses. For maintenance dosing, the highest dose requirements for keeping a patient in the therapeutic range are in men < 50 years old (median dose, 6.4 mg/d) and the lowest requirements are in women > 70 years old (median dose, 3.1 mg/d). Occasionally, patients need doses as high as 20 to 30 mg per day. Genetic testing for polymorphisms of the *CYP2C9* and *VKORC1* enzyme genes is available but despite extensive clinical trial testing, pharmacogenetic testing has not been shown to reduce the risk of thrombosis or bleeding.

Management of elevated INRs and bleeding

Several options exist to manage elevated INRs and bleeding that occur on VKAs, depending on the degree of INR elevation and the presence or absence of risk factors for bleeding and of active bleeding itself. A general management strategy is presented in Table 9-8 and

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Table 9-8 Management strategy for elevated INRs in patients on VKAs

INR	Bleeding?	Risk factors for bleeding?	Intervention
Supratherapeutic, but <5.0	No	No/yes	Lower or omit next VKA dose(s); reduce subsequent dose(s)
5.0-9.0	No	No	Omit next VKA doses; reduce subsequent dose; low-dose oral vitamin K accelerates INR drop but is not likely to improve clinical outcome
5.0-9.0	No	Yes	Vitamin K 1-2.5 mg orally
>9.0	No	No/yes	Vitamin K 2.5-5 mg orally
Serious bleed at any INR	Yes		Vitamin K 2.5-10 mg IV + PCCs (fresh frozen plasma can be used if PCCs unavailable)

PCC, prothrombin complex concentrate.

encompasses holding the next anticoagulant dose(s) and giving vitamin K. Giving too high a dose of vitamin K should be avoided if there is no major bleeding, because it reverses the INR completely and may make reanticoagulation more difficult. FFP can lower the INR to an extent. If complete or immediate INR reversal is needed, such as when treating a major bleeding episode, a prothrombin complex concentrate (PCC) is preferred over FFP, if available. PCCs are plasma-derived products from human donors that contain high concentrations of the vitamin K–dependent factors (ie, II, VII, IX, and X). They exist as *4-factor PCCs*, containing all vitamin K–dependent coagulation factors, and as *3-factor PCCs*, which contain relatively low concentrations of factor VII. The 4-factor products are capable of restoring individual clotting factor activity to nearly 100% within minutes of administration of a low-volume intravenous infusion. KCentra is the only 4-factor PCC available in the United States as of June 2021. Recombinant factor VIIa is not recommended in the management of VKA-associated hemorrhage.

Periprocedural interruption of VKA therapy

Whether there is a need to stop oral anticoagulant therapy before a surgical or radiological procedure depends on the bleeding risk associated with the procedure. How far in advance of the procedure to stop VKAs depends on the INR, the age of the patient, and the half-life of the VKA. Bridging therapy with a subcutaneous or intravenous anticoagulant is typically unnecessary but may be beneficial in patients whose thrombosis risk is very high (see https://thrombosiscanada.ca/clinicalguides).

Pediatric considerations

Warfarin is the most commonly used and studied VKA in children worldwide. Acenocoumarol is administered with high frequency in some European and South American countries, and phenprocoumon is the preferred VKA in some parts of Europe. The current therapeutic INR ranges for children are extrapolated from recommendations for adult patients, because no clinical trials have assessed the optimal INR range for children.

Warfarin is usually commenced at 0.1 to 0.2 mg/kg, capped at 5 mg maximal starting dose. Patients with liver impairment, or post-Fontan surgery, require lower doses.

Monitoring oral anticoagulant therapy in children is difficult and requires close supervision with frequent dose adjustments. Only 10% to 20% of children are safely monitored monthly. Studies in children comparing POC monitors to venipuncture INR confirm their accuracy and reliability. The major advantages of POC devices include reduced trauma of venipunctures, minimal interruption of school and work, ease of operation, and portability. However, all POC devices are operator dependent and considerable family education is required to ensure accurate use, and an ongoing quality assurance program is recommended.

VKAs are often avoided in infants for several reasons:

- The plasma levels of the vitamin K–dependent coagulation factors are physiologically decreased in comparison with adult levels.
- Infant formula is supplemented with vitamin K to prevent hemorrhagic disease, which makes formula-fed infants resistant to VKA.
- Breast milk has low concentrations of vitamin K, making breastfed infants sensitive to VKA, which can be compensated for by feeding 30 to 60 ml of formula each day.
- VKAs are available only in tablet form in most countries, thus being unsuitable for newborns even if suspended in water.
- VKA requirements change rapidly across infancy because of rapidly changing physiological values of the vitamin K–dependent coagulation proteins, and changes in diet.

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- There is little efficacy or safety information specific to VKA use in neonates.

However, for prosthetic valves, homozygous protein C deficiency and long-term therapy (beyond 3 to 6 months), VKA is probably superior to LMWH and can be managed in this age group by experienced teams and with adequate parental support.

Bleeding is the main complication of VKA therapy; however, in experienced hands, the bleeding rates are reported to be less than 0.5% per patient year.

Approximately 30% of teenage girls on VKA develop menorrhagia, and proactive management of menstrual bleeding (often involving gynecological services) and attention to iron status is critical. A high proportion of teenagers who start VKA during their teenage years develop clinical depression or anxiety related to the psychosocial challenges involved in lifestyle restrictions. Proactive psychological support of these patients is important. Nonhemorrhagic complications of VKA, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Reduced bone density in children on warfarin for more than 1 year has been reported in a number of studies and many programs routinely monitor bone density in all children on long-term VKA.

Patient and family education protocols are major factors in reducing bleeding events in children on VKA therapy.

Direct oral anticoagulants

DOACs are small molecule inhibitors of coagulation factor Xa (anti-Xa drugs) or thrombin (anti-IIa drugs). They share several desirable attributes: (1) rapid onset of action, (2) lack of need for routine monitoring of anticoagulant effect in most patients, (3) relatively few clinically important interactions with medications, (4) no dietary restrictions, and (5) short half-lives that simplify perioperative anticoagulation management. However, the dependence of some of these drugs on renal clearance limits their use in some patients. Four oral anti-Xa and 1 oral direct thrombin inhibitors are approved for various indications in the United States. Because the approved indications are expanding relatively rapidly as clinical trial data become available and are reviewed by the FDA, the reader is encouraged to obtain up-to-date approval status information when reading this section of this chapter. The names, molecular targets, and other pharmacologic properties of the 5 new oral anticoagulants furthest along in development are listed in Table 9-9, and include dabigatran, rivaroxaban, apixaban, edoxaban, and recently betrixaban. Rivaroxaban and dabigatran have now completed trials in children and can be used in accordance with the clinical trial protocols.

Management issues

Several issues are important in management of patients who are being treated with DOACs.

First, although routine monitoring of the anticoagulant effect of these drugs is not necessary, measurement of their anticoagulant effect is helpful in selected clinical situations. For example, laboratory measurement of anticoagulant effect may be helpful for a bleeding patient, a patient in whom treatment failure is suspected, or a patient for whom the risks and benefits of urgent surgery are being considered. Data on expected therapeutic plasma drug levels determined by clinical bleeding and clotting events and the performance of the various coagulation tests have been published elsewhere. The ideal test for dabigatran is the dilute thrombin time or an ecarin-based assay. For FXa inhibitors (apixaban, rivaroxaban, edoxaban, and betrixaban), an anti-Xa activity—calibrated to the drug being measured—is preferred over other options. Many, but not all, aPTT assays are prolonged by clinically relevant concentrations of dabigatran. The same is true of the PT for rivaroxaban. For both medication-test combinations, the clinician should be aware of the sensitivity of his or her own laboratory's assays before interpreting the results.

Second, a growing body of evidence suggests that for patients whose thrombosis risk is low or moderate, DOACs can be interrupted for brief periods (<5 days) with a very low risk of thrombotic complications. The duration of preprocedural interruption is typically 24 to 72 hours but depends on renal function and the risk of bleeding inherent to the planned surgery (see https://thrombosiscanada.ca/clinicalguides).

Although both major intracranial bleeding and fatal bleeding occur less frequently with DOACs than with warfarin, major bleeding in patients taking these drugs can occur. Specific antidotes—idarucizumab for dabigatran and andexanet alpha for direct factor Xa inhibitors—are approved for use in the United States and Europe. However, approval of andexanet alfa by both agencies is conditional and additional studies of efficacy are required. Phase 2 trials of ciraparantag, a small molecule reversal agent that binds to unfractionated heparin, LMWH, and DOACs are ongoing.

There is no evidence from either the pooled analyses of these trials or postapproval registry studies that major bleeding outcomes are worse in patients taking DOACs than in patients taking warfarin. Therapy with oral charcoal is appropriate in the patient who ingested the drug

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Table 9-9 Direct oral anticoagulants: selected pharmacologic properties and approval status in adults

Generic name	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Betrixaban
Brand name	Eliquis	Pradaxa	Lixiana, Savaysa	Xarelto	Bevyxxa
Target	FXa	FIIa	FXa	FXa	FXa
T_{max}(h)	1-3	1.25-3	1-2	2-4	3-4
Half-life (h) in patients with normal renal function	8-15	12-14	8-10	9-13	19-27
Effect of hepatic impairment	Mild to moderate hepatic insufficiency (Child-Pugh A or B): no evidence of a consistent change in exposure	Moderate hepatic insufficiency (Child-Pugh B): no evidence of a consistent change in exposure	Moderate hepatic insufficiency (Child-Pugh B): no evidence of a consistent change in exposure	Moderate hepatic impairment (Child-Pugh B): increased mean exposure by 2.3-fold	Not evaluated
Renal excretion, %	25	80	35-40	66	11
Effect of renal impairment	CrCL 30-50: 1.29-fold greater exposure	CrCL 30-50: 2.7-fold greater exposure	Not reported	CrCL 30-49: 1.5-fold greater exposure	60 to 90: 1.89-fold
	CrCL 15-29: 1.44-fold greater exposure	CrCL 10-30: 6-fold greater exposure (2-fold increase in the plasma half-life)		CrCL 15-29: 1.6-fold greater exposure	30 to 60 2.27-fold and 15 to 30 2.63-fold
Dosing frequency	Twice daily	Twice daily	Once daily	Once daily†	Once daily
Drug interactions	P-gp, CYP3A4	P-gp	P-gp	P-gp, CYP3A4	P-gp
Approval status as of February 2018 (United States)	Stroke prevention in AF; acute VTE treatment⋆ and secondary VTE prevention; primary VTE prevention after total knee or hip replacement	Stroke prevention in AF; acute VTE treatment‡ and secondary VTE prevention	Stroke prevention in AF; acute VTE treatment‡ and secondary VTE prevention	Stroke prevention in AF; acute VTE treatment†⋆ and secondary VTE prevention; primary VTE prevention after total knee or hip replacement	VTE prevention, moderate- and high-risk medically ill

AF, atrial fibrillation; CrCL, creatinine clearance (mL/min).

⋆Apixaban is given 10 mg twice daily for the first 7 days in patients with acute VTE.

†Rivaroxaban is given 15 mg twice a day for the first 21 days in patients with acute VTE.

‡For dabigatran and edoxaban a 5-day "lead-in" with heparin or low-molecular-weight heparin is required in the treatment of acute VTE.

within 2 hours of presentation with major bleeding. FFP would not be expected to have any efficacy. Rivaroxaban, apixaban, edoxaban, and betrixaban cannot be removed with dialysis because they are highly bound to plasma proteins. Preclinical data from animal models, healthy volunteers, and ex vivo coagulation experiments suggest that PCCs may be of some benefit, but these interventions should be reserved for truly dire circumstances.

Very few patients with a diagnosis of APS, cancer, or warfarin failure were included in the VTE treatment trials of DOACs. However, as mentioned, data exist on the noninferiority of edoxaban, apixaban, and rivaroxaban compared to LMWH, for the treatment of CAT and there is a signal for increased recurrent arterial thrombosis in high-risk APS patients. Because a study was stopped for increased thromboembolic events in the dabigatran arm compared to warfarin in a study of patients with mechanical prosthetic heart valves, DOACs should not be used to replace VKA treatment in a patient with a mechanical prosthetic heart valve.

Thrombolytic agents

A number of different thrombolytic (fibrinolytic) drugs are in clinical use, including streptokinase, urokinase, recombinant tPA, and tPA variants. All of them activate plasminogen to plasmin, which can then exert its thrombolytic effect on fibrin. In clinical practice, these drugs are used relatively rarely for venous thromboembolism because the associated risk of major bleeding is often not justified by the potential benefit. Massive PE and large

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iliofemoral DVT with phlegmasia are 2 potential situations for thrombolytics in VTE.

No study has compared the efficacy, safety, or cost of different thrombolytic agents in children. However, tPA has become the agent of choice in pediatric patients. There is minimal experience with other thrombolytic agents in children and little consensus in indications for thrombolysis, dose, mode of delivery, or duration of therapy, reflecting the lack of good-quality studies. At this time, there is no evidence to suggest that there is an advantage of local over systemic thrombolytic therapy in children with thrombotic complications.

Infants have a relative plasminogen deficiency compared to adults and common practice is to give FFP 10 ml/kg prior to tPa, in an effort to provide better plasminogen substrate for the tPa and to reduce bleeding through improved fibrinogen levels. Thrombolytics may not inhibit clot propagation, hence thrombin inhibition is required as adjunctive therapy. Concurrent low-dose UFH (10 U/kg/h) followed by therapeutic UFH is usually recommended.

Aspirin

Aspirin (acetylsalicylic acid) inhibits the enzyme cyclooxygenase-1 (COX-1), which is needed to form thromboxane A_2 in platelets. Thromboxane A_2 is normally released from platelet granules upon platelet adhesion and during platelet aggregation and serves as an agonist to activate, and thus recruit, other platelets to the platelet plug. Because platelets do not synthesize new cyclooxygenase and aspirin binds irreversibly to COX-1, full recovery of thromboxane production of the platelet pool after stopping aspirin takes approximately 10 days (ie, the platelets' life span). Recovery of platelet aggregation is quicker, however, occurring within 4 days of stopping aspirin, because thromboxane from newly synthesized platelets can activate aspirin-affected platelets. Complete inactivation of platelet COX-1 typically is achieved with a daily dose of 160 mg of aspirin. When used as an antithrombotic drug, aspirin is maximally effective at doses between 50 and 325 mg per day. In most clinical situations, higher doses increase the likelihood of toxicity (gastric ulceration and bleeding) but have not been consistently shown to improve efficacy.

In children, aspirin doses (when being used for antiplatelet therapy) vary from 1 to 5 mg/kg/d, with maximal dose of 100 mg/d. Gastrointestinal toxicity appears less in younger children. Reye syndrome was associated with doses above 40 mg/kg/d, so higher doses should be avoided.

Special populations

Women and girls

Unique features of estrogen-associated thrombosis are discussed previously. However, the management of anticoagulation in menstruating girls and women and requires special consideration independent of hormonal risk factors.

All forms of anticoagulation are associated with increased menstrual bleeding, though this is particularly true of rivaroxaban and perhaps less so of dabigatran. Regardless of choice of anticoagulant, a careful menstrual history at the time of anticoagulant initiation and discussion of the potential for increased bleeding are critical. Women who have a current or past history of heavy bleeding should be offered treatment, including the possibility of continuing established hormonal therapies while anticoagulated. Women who have no such history should be counseled that heavy bleeding may develop and advised to contact seek medical advice if they do. In women with known heavy bleeding, consideration should be given to checking a ferritin and offering iron support as indicated.

The hematologist should also discuss contraceptive options with all girls and women of reproductive age on anticoagulation. Because of the increased risk of thrombosis during all trimesters of pregnancy, known teratogenic risk with VKAs, and unknown risks with other oral anticoagulants, pregnancy would be ideally deferred until completion of anticoagulation therapy. However, this may not be feasible for women on long-term anticoagulation. Ideally all women would receive preconception counseling, including a discussion of switching from an oral agent to LMWH, which is safe in pregnancy, versus continuing the current therapy until a positive pregnancy test is achieved. During all discussions it is important to keep in mind that pregnancy is a higher-risk state than hormonal contraceptive use. Anticoagulation prophylaxis may be required in the setting of stimulated egg harvest and assisted reproduction.

Transgender patients

Because the most immediately apparent risk associated with gender-affirming hormonal therapies is that of thrombosis, the hematologist needs to have at least a basic familiarity with these therapies and the associated risks. Risk can vary considerably with route and formulation of therapies. For transgender women, hormone replacement therapies containing estradiol rather than ethinylestradiol (more commonly used in contraceptives) are associated with lower risk of VTE, as is the transdermal route of administration. This risk may increase after 2 years of

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therapy whereas the risk of stroke remains roughly similar to that of cisgender men for the first 6 years of therapy, after which point the risk can increase as much as tenfold. Risk of myocardial infarction remains comparable to that of cisgender men (although higher than that of cisgender women). If a VTE event does develop, the importance of continuing hormonal therapy for mental well-being must be kept in mind and, as with cisgender women who may choose to continue estrogen-based therapies after a VTE event, continued use of therapeutic anticoagulation is advisable.

For transgender men using testosterone therapy, the risk of VTE appears to be low and comparable to that of cisgender men and cisgender women. Similarly there is no convincing evidence of increased rates of arterial events.

Thrombophilia testing is not recommended in advance of hormonal therapy for either cisgender men or cisgender women. In all cases the lowest dose and safest formulation/route that can successfully meet goals of therapy is encouraged.

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